# Development of an Intramolecular Alkene Aminocyanation Reaction and Progress Toward the Total Synthesis of Drimentine C

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# Dedication

*to my husband, Chris Pound*

# Abstract

**Part I:** The first part of this Thesis describes our work towards transition metal-catalyzed N–CN bond activation and the serendipitous discovery of a metal-free, Lewis acid-promoted intramolecular aminocyanation reaction. This transformation involves the N–CN σ-bond cleavage of a cyanamide and addition across a tethered alkene resulting in indolines bearing a quaternary stereocenter and a versatile cyano group. In Part I, the reaction optimization and the scope of substrates are presented, and initial mechanistic investigations are discussed.

**Part II:** The drimentines are a family of nine alkaloids isolated from two *Actinomycete* strains characterized by a novel core structure consisting of condensed pyrroloindoline and diketopiperazine moieties tethered to a sesquiterpene through a methylene bridge. In preliminary assays of biological activity, the drimentines were found to exhibit weak to moderate cytotoxicity and antibacterial activity. However, due to their unique structure, the drimentines are of interest for further study. We propose two routes for the total synthesis of drimentine C. The first route, detailed in Chapter 2, highlights the utility of C–CN bond activation. The proposed key step is a palladium-catalyzed asymmetric cyanoamidation reaction wherein the C–CN σ-bond of a cyanoformamide is cleaved and added across a pendant alkene resulting in an oxindole with a newly-formed all-carbon quaternary stereocenter. The cyano group can then be elaborated into the pyrroloindoline

ring present in drimentine C. The second proposed route builds drimentine C from naturally-occurring, L-tryptophan, L-proline, and (+)-sclareolide. Three methodologies for construction of the key C–C σ-bond between the pyrroloindoline and sesquiterpene moieties are presented: (1) organocuprate addition to a cyclopropylazetoindoline intermediate; (2) nickel-catalyzed reductive cross-coupling; and (3) photoredox-catalyzed α-alkylation of an enamine. Progress toward the total synthesis of drimentine C via this convergent route is disclosed in Chapter 4.

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# List of Abbreviations

| | |
|---|---|
| 2M3BN | 2-methyl-3-butenenitrile |
| 3PN | 3-pentenenitrile |
| Ac | acetyl |
| acac | acetylacetonate |
| AdN | adiponitrile |
| AIBN | 2,2′-azobis(2-methylpropionitrile) |
| Anis | anisyl |
| Ar | aryl |
| aq. | aqueous |
| BDE | bond dissociation energy |
| BINOL | 1,1′-bi-2-naphthol |
| Bn | benzyl |
| Boc | *tert*-butyloxycarbonyl |
| BPhen | bathophenanthroline |
| bpy | 2,2′-bipyridine |
| Bu | butyl |
| *s*Bu | *sec*-butyl |
| *t*Bu | *tert*-butyl |
| CD | circular dichroism |
| CI | chemical ionization |
| cod | 1,5-cyclooctadiene |
| coe | cyclooctene |
| COSY | correlated spectroscopy |
| Cp | cyclopentadienyl |
| Cp* | pentamethylcyclopentadiene |

| | |
|---|---|
| Cy | cyclohexyl |
| DCE | dichloroethane |
| dba | dibenzylideneacetone |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| decalin | decahydronaphthalene |
| DFT | density functional theory |
| DIBAL | diisobutylaluminum hydride |
| diglyme | diethylene glycol dimethyl ether |
| DMA | *N*,*N*-dimethylacetamide |
| DMAP | 4-(dimethylamino)pyridine |
| DME | dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMPU | 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone |
| DMSO | dimethylsulfoxide |
| DPEphos | (oxydi-2,1-phenylene)bis(diphenylphosphine) |
| dppb | 1,4-bis(diphenylphosphino)butane |
| dr | diastereomeric ratio |
| dppe | ethylenebis(diphenylphosphine) |
| ECD | electronic circular dichroism |
| EDC•HCl | *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride |
| *ee* | enantiomeric excess |
| EoY | Eosin Y |
| ESI | electrospray ionization |
| equiv | equivalent |
| Et | ethyl |
| FG | functional group |
| GCMS | gas chromatography mass spectrometry |
| glyme | 1,2-dimethoxyethane |

| | |
|---|---|
| HATU | 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexaflurorphosphate |
| Hex | hexyl |
| HMBC | heteronuclear multiple bond correlation |
| HMDS | hexamethyldisilazane |
| HMPA | hexamethylphosphoramide |
| HOBt•$H_2O$ | 1-hydroxybenzotriazole hydrate |
| HPLC | high performance liquid chromatography |
| Hsp90 | heat shock protein 90 |
| HSQC | heteronuclear single quantum coherence |
| LC | liquid chromatography |
| LED | light-emitting diode |
| *m* | meta |
| Me | methyl |
| Mes | mesitylene |
| MOM | methoxy methyl |
| MPLC | medium pressure liquid chromatography |
| MS | mass spectrometry |
| μ-wave | microwave |
| NADH | nicotinamide adenine dinucleotide |
| NBS | *N*-bromosuccinimide |
| NCTS | *N*-cyano-*N*-phenyl-*para*-toluenesulfonamide |
| NFSI | *N*-fluorobenzenesulfonimide |
| NMI | *N*-methylimidazole |
| NMP | *N*-methyl-2-pyrrolidinone |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| NOESY | nuclear Overhauser spectroscopy |

| | |
|---|---|
| Nixantphos | 4,6-bis(diphenylphosphino)phenoxazine |
| Ns | *para*-nitrobenzenesulfonyl (nosyl) |
| *o* | ortho |
| *p* | para |
| PCC | pyridinium chlorochromate |
| Ph | phenyl |
| Phth | phthaloyl |
| Phen | phenanthroline |
| PIDA | (diacetoxyiodo)benzene |
| pin | pinacol |
| PPTS | pyridinium *para*-toluenesulfonate |
| ppy | 2-phenylpyridine |
| Pr | propyl |
| *i*Pr | *iso*-propyl |
| PTFE | polytetrafluoroethylene |
| PTSA | *para*-toluenesulfonic acid |
| py | pyridine |
| Pybox | pyridine bisoxazoline |
| Pyox | pyridine oxazoline |
| qNMR | quantitative nuclear magnetic resonance |
| RB | Rose Bengal |
| rt | room temperature |
| sat. | saturated |
| SET | single-electron transfer |
| sp. | species |
| tbbpy | 4,4′-di-*tert*-butyl-2,2′-bipyridine |
| tbppy | 2-(4-*tert*-butyl)phenyl)pyridine |
| TBS | *tert*-butyldimethylsilyl |

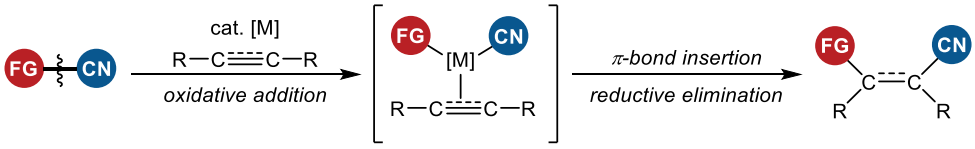
| | |
|---|---|
| TCNEO | tetracyanoethyleneoxide |
| TDDFT | time-dependent density functional theory |
| TEMPO | (2,2,6,6-tetramethyl-1-piperidinyl)oxyl |
| terpy | terpyridine |
| Tf | triflyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TMS | trimethylsilyl |
| TOCSY | total correlation spectroscopy |
| Ts | tosyl |
| Xantphos | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene |
| (*R*,*R*)-ChiraPhos | (2*R*,3*R*)-(+)-2,3-bis(diphenylphosphino)butane |
| (*R*,*R*)-*i*Pr-Foxap | (*R*)-1-(diphenylphosphino)-2-[(*R*)-4-isopropyloxazolin-2-yl]ferrocene |
| (*S*,*S*,*R*,*R*)-TangPhos | (1*S*,1*S*′,2*R*,2*R*′)-1,1′-di-*tert*-butyl-(2,2′)-diphospholane |

# Part I: Development of an Intramolecular Aminocyanation of Alkenes

# Chapter 1: Lewis Acid-Promoted Intramolecular Aminocyanation of Alkenes

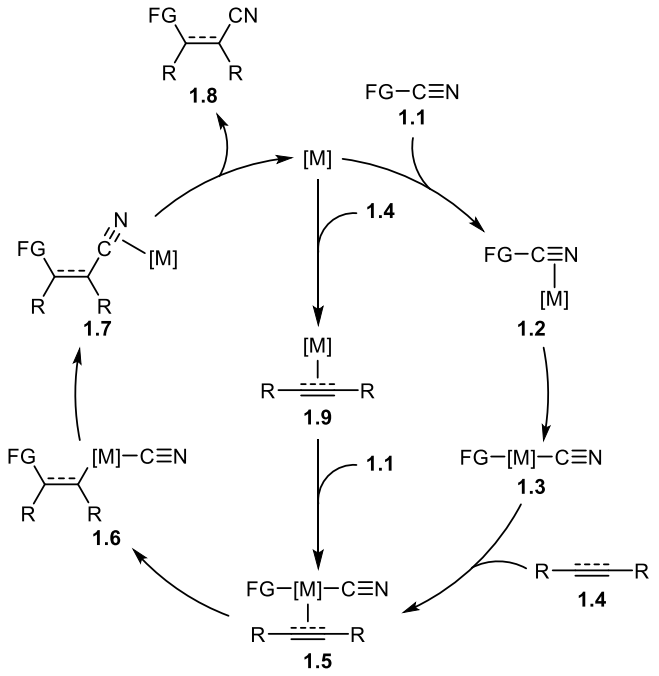
## 1.1 Introduction

A continuing goal of organic chemistry is to develop efficient methodologies that rapidly increase molecular complexity while producing minimal waste. The bond activation reaction class has made headway toward this goal. Cyanofunctionalization is a class of reactions where an element–cyano σ-bond (FG–CN) is cleaved and added across an unsaturated carbon–carbon (C–C) bond (Scheme 1.1). These reactions construct highly functionalized nitriles in an atom-economical fashion.[1] The synthetic versatility of the cyano group[2] as well as the continuing demand for methods to prepare functionalized nitriles[3] make this a highly useful methodology. Additionally, the functional group added could serve as a handle for further functionalization including cross-coupling reactions.




**Scheme 1.1** Catalytic cyanofunctionalization

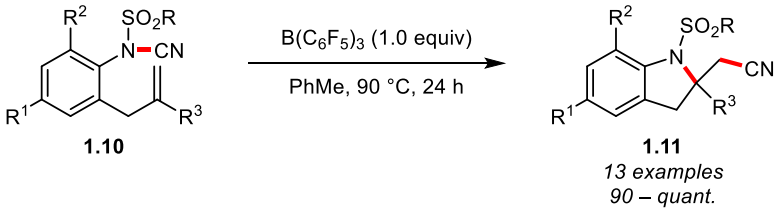
Cyanofunctionalization is typically catalyzed by transition metals. A low-valent metal complex coordinates to nitrile **1.1** forming complex **1.2** (Scheme 1.2). Oxidative addition of the FG–CN bond produces FG–M–CN complex **1.3**. This coordinates to the π-bond of olefin **1.4** forming complex **1.5**. Migratory insertion yields adduct **1.5**, and C–CN bond-forming reductive elimination releases nitrile **1.8** and regenerates the active catalyst. Alternatively, the low-valent metal complex can pre-coordinate to olefin **1.4** resulting in adduct **1.9** then undergo oxidative addition with nitrile **1.1** to form complex **1.5**.




**Scheme 1.2** General mechanism of cyanofunctionalization

A wide variety of cyanofunctionalizations have been realized including silylcyanation, germylcyanation, borylcyanation, thiocyanation, and bromocyanation. Carbocyanation, the activation of C–CN σ-bonds, is of great interest to the chemical community and will be discussed in depth in Chapter 3. Much rarer are O–CN and N–CN bond cleavage (oxycyanation and aminocyanation, respectively). However, aminocyanation in particular would be a powerful methodology, allowing straightforward access to synthetically-relevant blocks, 1,3-diamines and β-amino acids.[4]

This Chapter will briefly discuss transition metal-catalyzed cyanofunctionalization highlighting oxycyanation and aminocyanation. It will then detail the efforts toward developing N–CN bond activation using transition metal catalysis and the serendipitous discovery of a novel Lewis acid-promoted aminocyanation reaction, which resulted in a publication in 2014 (Scheme 1.3).[5]




**Scheme 1.3** Lewis acid-promoted intramolecular aminocyanation of alkenes

## 1.2 Background on Cyanofunctionalization

This section will focus on a brief review of cyanofunctionalization reactions starting with heteroatom–CN bond activation followed by O–CN and N–CN bond activation using transition metal-catalysis.

### 1.2.1 Cyanofunctionalization

The oxidative addition of heteroatom–CN σ-bonds is more facile than that of C–CN σ-bonds. This is evidenced by the lower bond dissociation energies (BDEs) and the longer bond lengths for these bonds, shown in Table 1.1.[6] Additionally, while C–CN bond activation is promoted by Lewis acid catalysis, it is often not required for other cyanofunctionalizations.

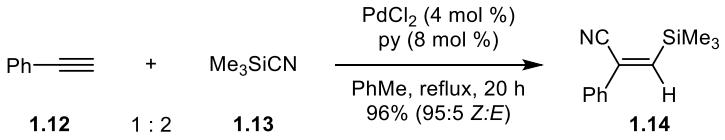
**Table 1.1** Selected Bond Dissociation Energies and Bond Lengths

| Entry | Bond | Bond Dissociation Energy (kcal $mol^{-1}$)[a] | Bond Length (Å)[b] |
|---|---|---|---|
| 1 | H–CN | 129 | 1.06 |
| 2 | C–CN | 124 | 1.87 |
| 3[c] | O–CN | 85–190 | 1.27[d] |
| 4 | N–CN | 119 | 1.38[e] |
| 5 | S–CN | 97 | ca. 1.80 |
| 6 | Br–CN | 87 | 1.79 |

| | | | |
|---|---|---|---|
| 7 | B–C | 85 | ca. 1.49 |
| 8 | Si–C | 104 | ca. 1.87 |
| 9 | Ge–C | ca. 57 | ca. 1.95 |

[a] Extracted from: Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: BocaRaton, FL, 2007 and references cited therein. [b] Extracted from: NIST Computational Chemistry Comparison and Benchmark Database. [c] Estimated values between C–O and C=O bonds. [d] From: Kutschabsky, L.; Schrauber, H. *Krist. Tech.* **1973**, *8*, 217. [e] From: Cunningham, I. D.; Light, M. E.; Hursthouse, M. B. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1999**, *55*, 1833.

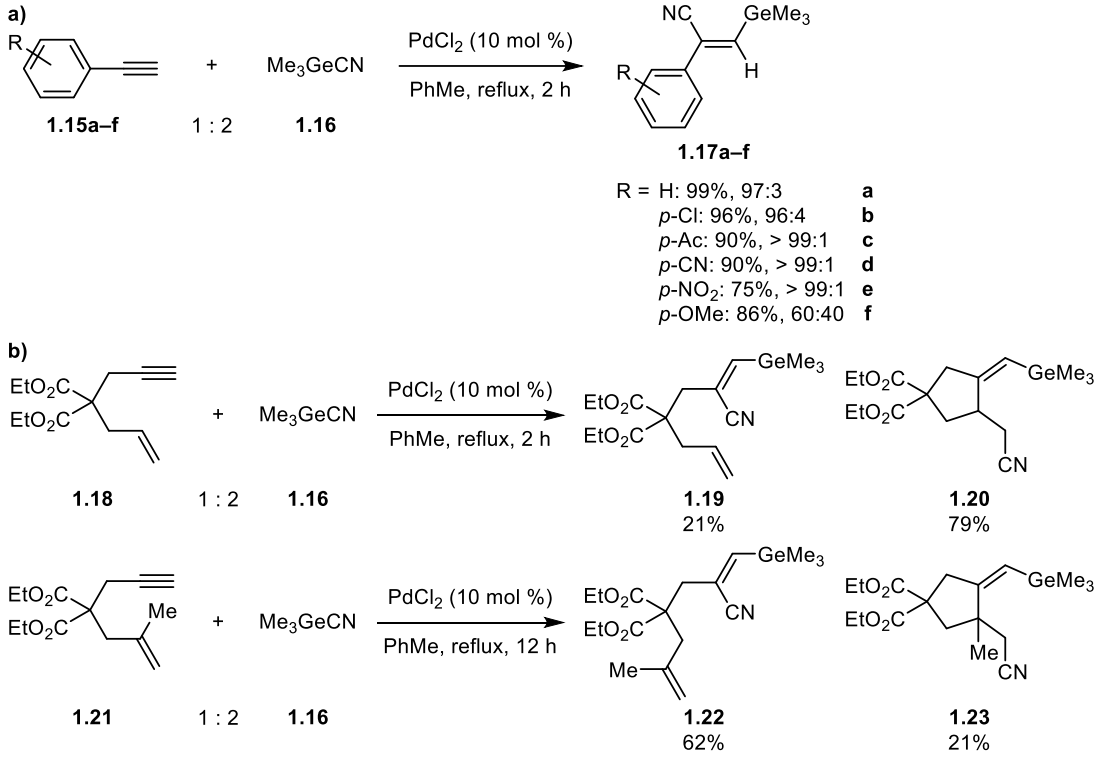
Silylcyanides serve as less-toxic cyanide surrogates. The first report of Si–CN bond activation was published by Chatani et al.[7] in 1988. Under palladium catalysis, phenylacetylene **1.12** underwent silylcyanation with trimethylsilylcyanide **1.13** producing vinylsilane **1.14** in 95% yield (Scheme 1.4). The regioselectivity favored the formation of *Z*-adducts. However, when using substituted phenylacetylenes, the selectivity for *Z*-product decreased in the order of *para* > *meta* > *ortho*. Both aromatic and heteroaromatic acetylenes were tolerated in this reaction. Dicyanation[8] and intramolecular[9] variants have been developed; however, these follow mechanisms different from that shown in Scheme 1.2 and will not be discussed.




**Scheme 1.4** Palladium-catalyzed silylcyanation of alkynes

In 1990, Chatani and coworkers[10–11] extended the cyanofunctionalization reactions from silylcyanation to germylcyanation. Heating terminal acetylenes **1.15a–g** and trimethylgermycyanide **1.16** in toluene with a catalytic amount of $PdCl_2$ produced *Z*-vinylgermanes in good to excellent yields (75–99%) (Scheme 1.5a). The trimethylgermyl

group was added selectively to the terminal alkyne carbon. Electron-withdrawing groups and electron-neutral groups on the phenyl ring were compatible with the reaction; however, electron-donating groups led to decreased selectivities (**1.17f**).

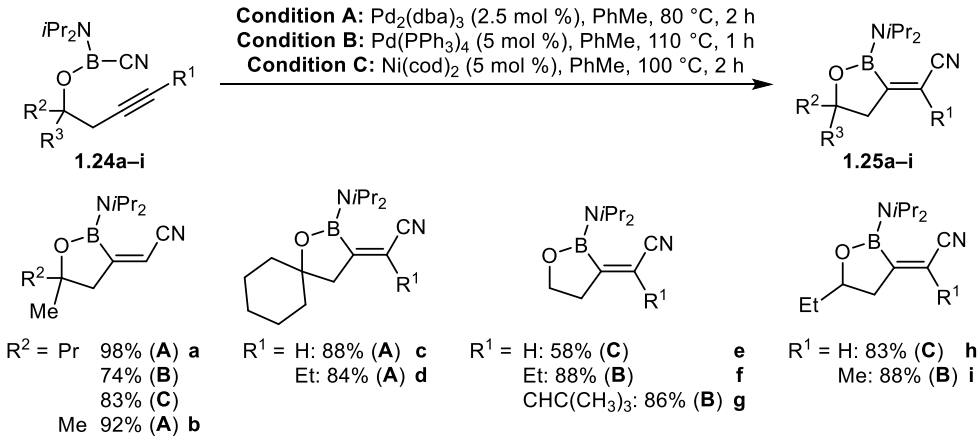



**Scheme 1.5** Palladium-catalyzed germylcyanation of alkynes: a) Phenylacetylene scope; b) Reaction of 1,6-enynes

The germylcyanation reaction with 1,6-enynes was examined (Scheme 1.5b). When subjected to the reaction conditions, addition of **1.16** occurred selectively at the alkyne of **1.18**. Both the direct addition product **1.19** and an unexpected cyclized product **1.20** were isolated in 21% and 79% yield, respectively. Cyclized product **1.20** was rationalized to arise from alkene insertion into the alkenylpalladium cyanide complex generated from the initial germylpalladation. When 1,6-enyne **1.21** bearing a more substituted alkene was subjected to the reaction conditions, the cyclization process was much slower. After 12 hours, **1.22** was obtained in 62% yield, and **1.23** was obtained in

21% yield.

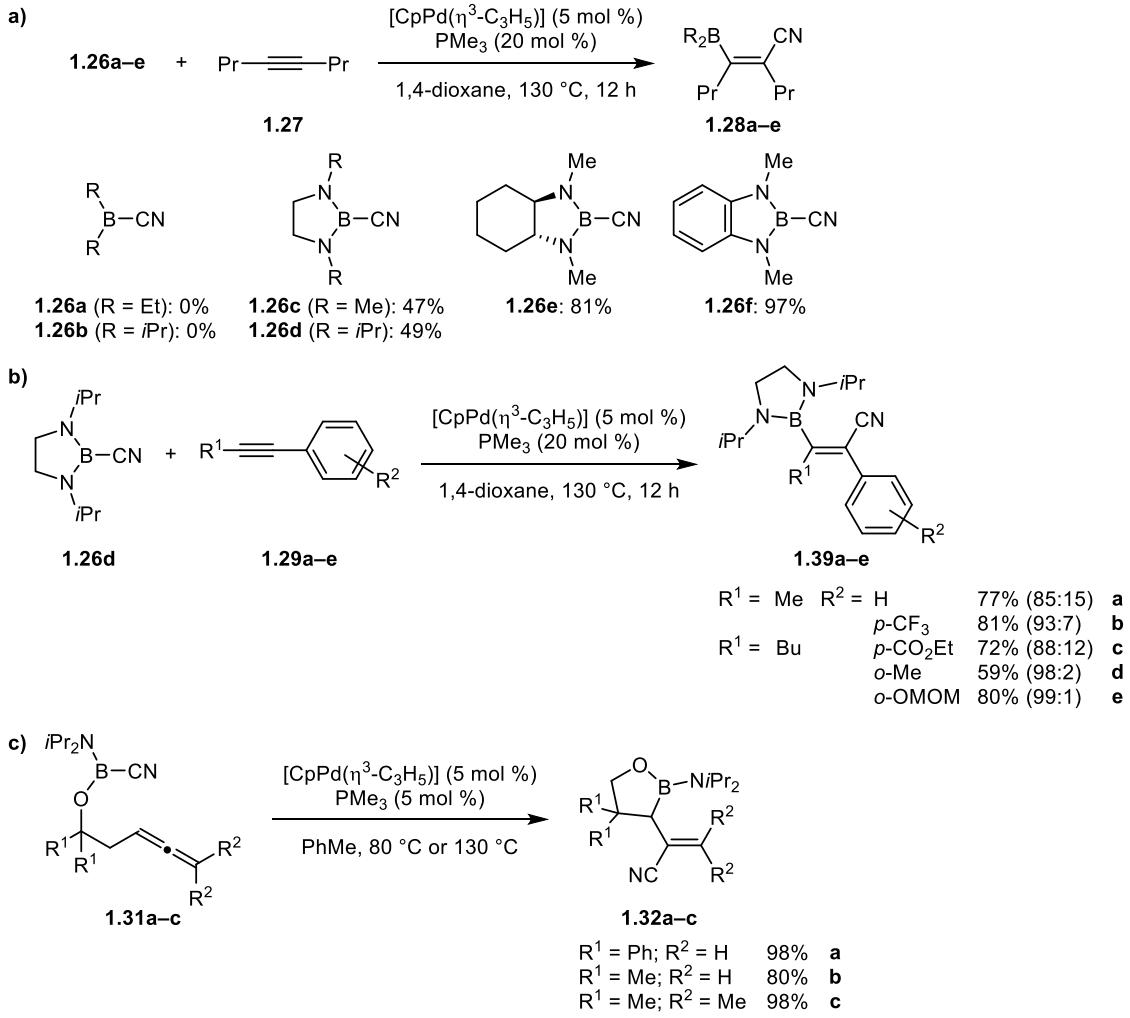
The development of methods to prepare boron derivatives is of great importance because of their functionality in Suzuki cross-coupling reactions. In 2002, Suginome et al.[12] reported the first B–CN bond cleavage in the context of a Strecker-type aminative cyanation of aldehydes and ketones. They were able to apply this concept to the transition metal-catalyzed cyanoboration of C–C unsaturated bonds. Treatment of cyanoboryl ether **1.24a** (prepared from the corresponding homopropargylic alcohol and diaminocyanoborane) with palladium or nickel catalysis resulted in intramolecular cyclization to **1.25a** (Scheme 1.6).[13–14] This proceeded in a regioselective 5-*exo*-fashion to give the *cis*-adduct. $Pd_2(dba)_3$ was the most efficient catalyst for this substrate providing **1.25a** in 98% yield after reaction at 80 °C for 2 hours in toluene (condition A). This catalyst system was optimal for cyanoboryl ethers prepared from *tert*-homopropargylic alcohols (**1.24a–d**). Heating $Pd(PPh_3)_4$ at 110 °C for 1 hour in toluene (condition B) was the best catalyst system for cyanoboryl ethers with internal alkynes prepared from *prim*- and *sec*-homopropargylic ethers (**1.24f, g,** and **i**). When using cyanoboryl ethers prepared from terminal alkynes derived from *prim*- and *sec*-homopropargylic ethers (**1.24e** and **h**), heating with $Ni(cod)_2$ in toluene at 100 °C for 2 hours (condition C) provided the best yield of **1.25**.




**Scheme 1.6** Palladium- and nickel-catalyzed intramolecular borylcyanation of alkynes

Initial attempts at an intermolecular variant of borylcyanation using bis(dialkylamino) cyanoboranes **1.26a** and **1.26b** had been unsuccessful (Scheme 1.7a).[13] However, when Suginome and Murakami et al.[15] attempted borylcyanation using ethylenediamine-derived cyanoboranes **1.26c–f**, the reaction proceeded. Heating **1.26** and 4-octyne **1.27** with [CpPd($\eta^3$-$C_3H_5$)] (5 mol %) and $PMe_3$ (20 mol %) in 1,4-dioxane at 130 °C for 12 h provided α,β-unsaturated β-boryl nitriles **1.28a–e** in moderate yields. Addition to the alkene occurred exclusively as *cis*-addition. When unsymmetrical alkenes were used, the regioselectivity of the reaction depended on steric difference between the two substituents. The major product had the cyano group attached to the same carbon as the aryl group (Scheme 1.7b).

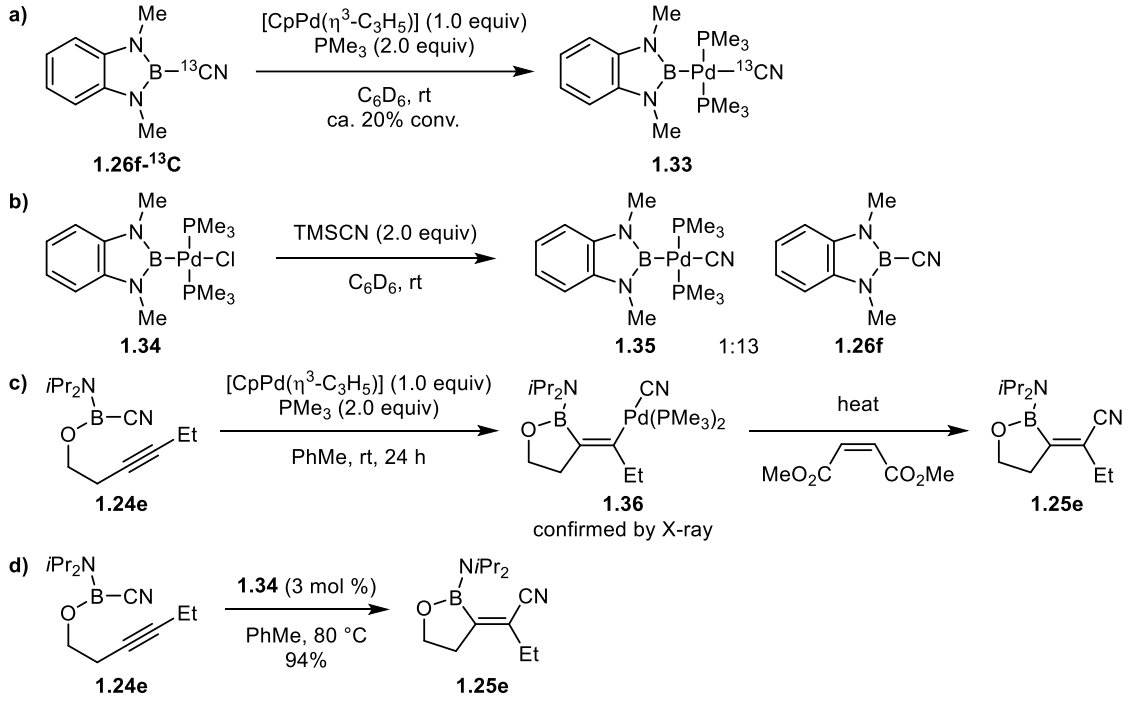
In 2009, Suginome et al.[16] reported that allenes could be used as alkyne surrogates in the intramolecular borylcyanation reaction. When aminocyanoboryl ether **1.31a** was heated with [CpPd($\eta^3$-$C_3H_5$)] (5 mol %) and $PMe_3$ (5 mol %) in toluene at 80 °C, allylborane **1.32a** was produced in 98% yield (Scheme 1.7c). Addition had occurred at the internal alkene with C–CN bond formation at the central carbon of the allene. Aminocyanoboryl ethers **1.31b** and **1.31c** bearing aliphatic groups adjacent to the boryl ether required higher reaction temperatures (130 °C) providing allylboranes **1.32b** and **1.32**c in 80% and 98% yield, respectively.




**Scheme 1.7** Palladium-catalyzed intermolecular borylcyanation: a) alkynes; b) unsymmetrical alkynes; c) allenes

Mechanistic experiments on the borylcyanation reaction were conducted to gain understanding about the proposed B–CN bond cleavage event.[17] When $^{13}$C-labeled cyanoborane **1.26f-$^{13}$C** was subjected to stoichiometric [CpPd($\eta^3$-$C_3H_5$)] and $PMe_3$, palladium complex **1.33** was produced (Scheme 1.8a). When this complex was treated with trimethylsilyl cyanide, it underwent reductive elimination to **1.26f** (Scheme 1.8b). This suggested that oxidative addition of the B–CN bond was reversible. When cyanoborane **1.24e** was subjected to the stoichiometric reaction conditions, palladium

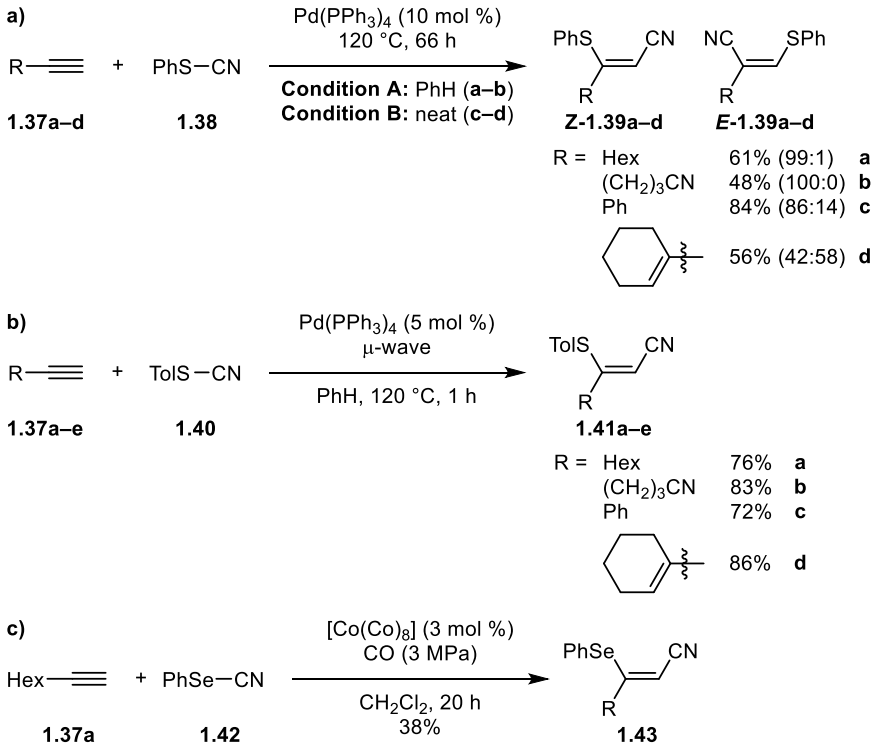
complex **1.36** was observed and confirmed by X-ray (Scheme 1.8c). It underwent reductive elimination with dimethyl maleate and heat to **1.25e**. Finally, treatment of **1.24e** with palladium complex **1.34** also provided **1.25e** (Scheme 1.8d). These results were all consistent with the proposed mechanism where palladium first complexes to the alkyne, the B–CN σ-bond is cleaved by oxidative addition, the boryl group inserts into the alkene, and the resulting alkene is reductively eliminated.




**Scheme 1.8** Palladium-catalyzed borylcyanation mechanistic experiments

In 2006, Nomoto and Ogawa et al.[18] reported the first example of transition metal-catalyzed thiocyanation of alkynes. Using zero-valent $Pd(PPh_3)_4$ (10 mol %), 1-octyne **1.37a** underwent reaction with thiocyanate **1.38** to produce (*Z)*-3-phenylthionon-2-enenitrile **1.39a** in good yield (61%) and excellent regioselectivity (99:1) (Scheme 1.9a). The reaction was greatly influenced by the solvent used. While the use of MeCN resulted in low yields, benzene provided thiocyanation product **1.39a** in higher yields. The thiocyanation of phenylacetylene **1.37c** was sluggish when conducted in benzene;

however, when the reaction was conducted neat, the efficiency was much improved. Product **1.39c** was obtained in 84% yield.



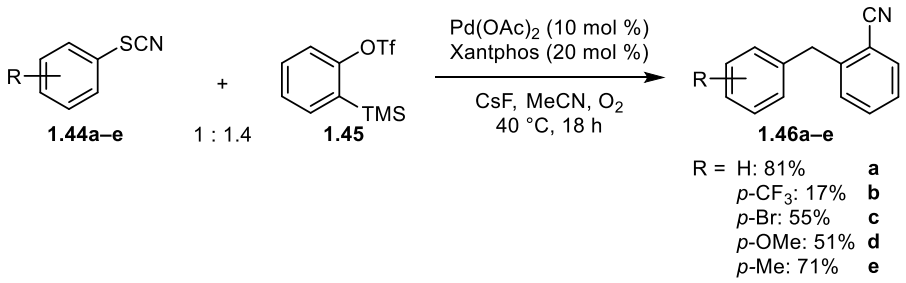

**Scheme 1.9** Intermolecular cyanofunctionalization of alkynes: a) palladium-catalyzed thiocyanation; b) with microwave irradiation; c) cobalt-catalyzed selenocyanation

Chung et al.[19] improved on the thiocyanation of alkynes by using microwave irradiation. 1-Octyne **1.37a** and 4-tolyl thiocyanate **1.40** were irradiated with microwave radiation in the presence of $Pd(PPh_3)_4$ and benzene (Scheme 1.9b). It was found that the loading of catalyst could be reduced from 10 mol % to 5 mol %. Additionally, the reaction time could be shortened from 66 hours to 1 hour with an improvement in yield. Only the *Z*-isomer was isolated from all reactions.

The thiocyanation of alkynes was expanded to selenocyanation by Ogawa et al.[20] Using $[Co_2(CO)_8]$ as the catalyst, 1-octyne **1.37a** underwent selenocyanation with phenyl selenocyanate **1.42** (Scheme 1.9c). This was conducted under a pressure of carbon

monoxide. Thiocyanation product **1.43** was obtained in moderate yield but excellent regioselectivity.

Werz et al.[21] recently reported the insertion of arynes into the S–CN bond of aryl thiocyanates. Heating thiocyanate **1.44a** and benzyne precursor **1.45** with $Pd(OAc)_2$ (10 mol %), Xantphos (20 mol %), and cesium fluoride in acetonitrile produced 1,2-thiobenzonitrile **1.46a** in 10–30% yields; the major byproduct was a diphenylthioether. By using an oxygen atmosphere, the yield of 1,2-thiobenzonitrile **1.46a** was increased to 81% and the production of diphenylthioether was minimized. Other common oxidants only suppressed formation of **1.46**. Electron-withdrawing substituents on the thiocyanate were detrimental to reactivity; **1.44b** provided **1.46b** in only 17% yield. The presence of halogens on the thiocyanate aromatic ring had only a small effect on reactivity (**1.46c**: 55%). Thiocyanates with electron-donating substituents (**1.44d–e**) provided thiocyanation products in good yields (**1.46d**: 51%; **1.46e**: 71%). The authors proposed that oxidative addition of the thiocyanate into the palladium complex occurred first. The resulting palladium complex coordinated to the benzyne formed from reaction of **1.45** with CsF. Migratory insertion and reductive elimination provided **1.46** and regenerated the low-valent palladium complex.



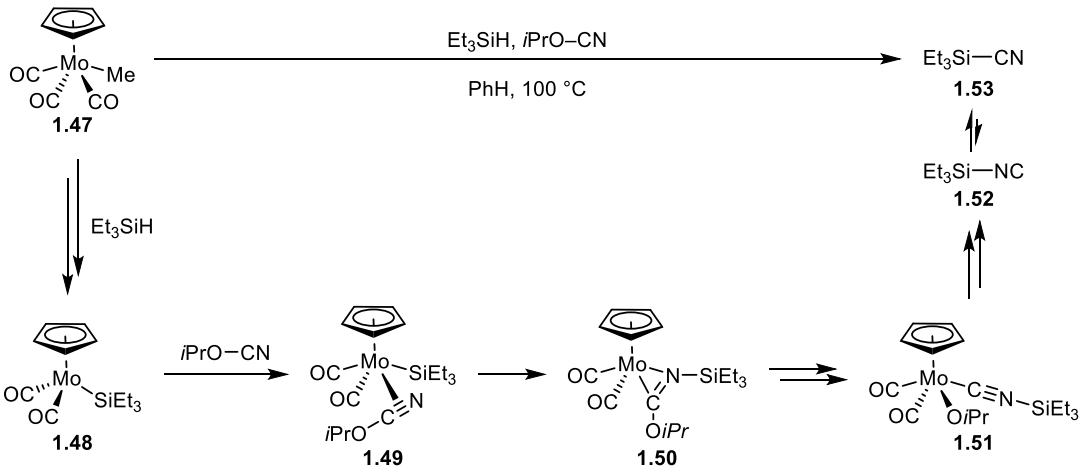

**Scheme 1.10** Palladium-catalyzed intermolecular thiocyanation of benzyne

### 1.2.2 Oxycyanation

Oxycyanation is more difficult to achieve than the previously discussed cyanofunctionalizations because the O–CN bond of cyanates has double bond character

(see Table 1.1). For example, the O–CN bond length of 2-chloro-5-cyanato-1,3-dimethylbenzene is 1.27 Å.[22] This lies between a typical O–CN single bond (1.42–1.44 Å) and a typical O=CN double bond (1.19–1.22 Å).[23]

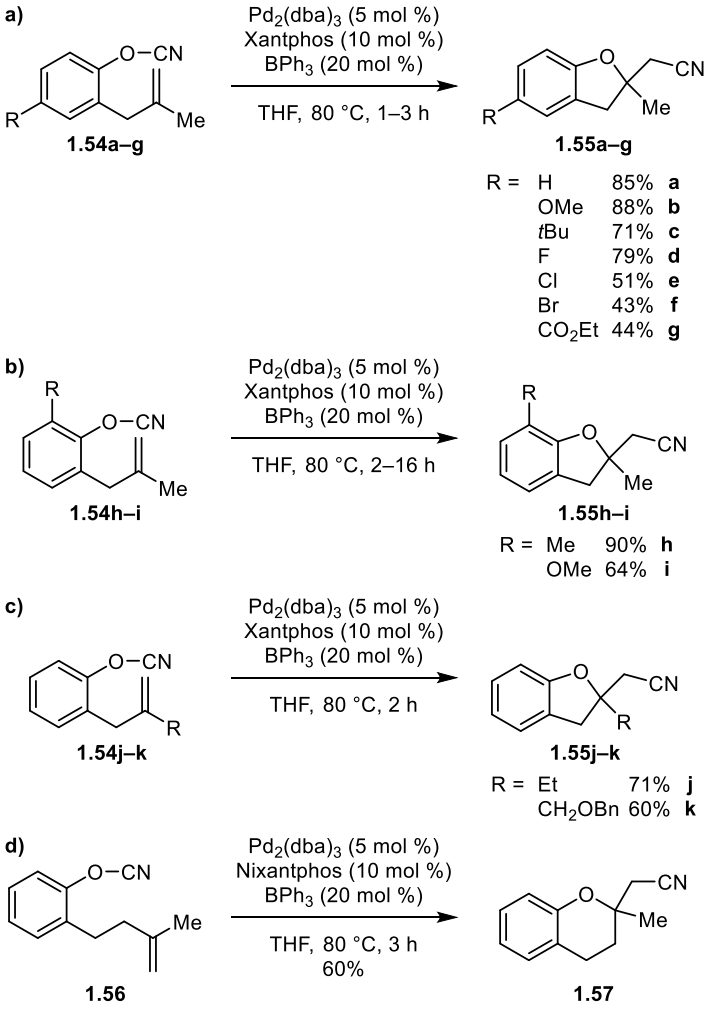
Nakazawa et al.[24] demonstrated that O–CN σ-bonds could be cleaved by transition metal complexes. Molybdenum methyl complex (**1.47**) with triethylsilane cleaved the O–CN bond of isopropyl cyanate, providing triethylsilyl cyanide (**1.53**). Density functional theory (DFT) calculations suggested that molybdenum methyl complex **1.47** reacted with triethylsilane to produce complex **1.48**. This coordinated to isopropyl cyanide to give $\eta^2$-complex **1.49**. The key step was migration of the silyl group to the nitrogen atom, which generated *N*-silyl $\eta^2$-imidato complex **1.50** followed by complex **1.51**. Reductive elimination produced triethylsilyl isocyanide **1.52**, which isomerized to **1.53**. A similar transformation using an iron-silyl complex was later described.[25]




**Scheme 1.11** O–CN bond cleavage by a molybdenum complex

In 2012, Nakao et al.[26] published a seminal paper on the intramolecular oxycyanation of alkenes. Using cooperative palladium- and Lewis acid-catalysis, the O–CN bond of cyanate **1.54a** was cleaved and added across the pendant alkene to generate dihydrobenzofuran **1.55a**, which bore an oxy-quaternary stereocenter and a cyano group

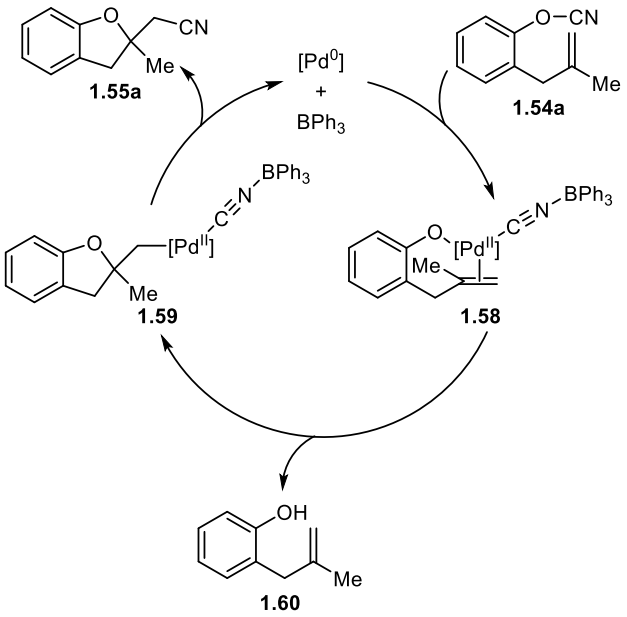
(Scheme 1.12a). The combination of $Pd_2(dba)_3$ and Xantphos was particularly effective; other catalysts produced mainly decyanation of **1.54a**. The effectiveness of Xantphos was due to its large bite-angle. Lewis acid was necessary; without it, poor conversion of **1.54a** occurred. Of the Lewis acids tested, $BPh_3$ was the most effective; other Lewis acids provided modest yields of **1.55a** at best. Using the optimized reaction conditions, dihydrobenzofuran **1.55a** was generated from **1.54a** in 85% yield.




**Scheme 1.12** Palladium/Lewis acid-catalyzed intramolecular oxycyanation of alkenes

A variety of cyanates with substituents *para*- to the cyanate group were compatible with the optimized reaction conditions. Substrates with electron-donating substituents (**1.54b–c**) provided dihydrobenzofurans **1.55** in better yields (88% and 71%) than substrates with electron-withdrawing substituents (**1.54d–g**, 44–79%). Notably, the O–CN σ-bond was selectively activated over an Ar–Br bond (**1.55f**, 43%). Substituents at the *ortho*-position were also well tolerated (Scheme 1.12b); cyanates **1.54h** and **1.54i** underwent the reaction, producing dihydrobenzofurans **1.55h** and **1.55i** in 90% and 64% yield, respectively. Changing the alkyl group at the double bond provided **1.55j** and **1.55k** in 71% and 60% yield, respectively (Scheme 1.12c). Six-membered ring formation was successfully accomplished using **1.56** (Scheme 1.12d). For this reaction, Nixantphos, which has a larger bite angle, was used as the ligand in place of Xantphos, providing **1.57** in 60% yield.

While the detailed mechanism has yet to be studied, it is speculated to proceed similar to the general mechanism for cyanofunctionalization. Lewis acid-promoted oxidative addition of the O–CN σ-bond of **1.54a** to low-valent palladium generates complex **1.58** (Scheme 1.13). Alkene insertion occurs in a 5-*exo*-trig fashion, which produces alkylpalladium(II) cyanide complex **1.59**. Reductive elimination of dihydrobenzofuran **1.55a** regenerates the active catalyst. The large bite angle of Xantphos presumably accelerates alkene insertion and reductive elimination. The decyanation byproduct **1.60** occurs from decomposition of complex **1.58**.




**Scheme 1.13** Catalytic cycle for palladium/Lewis acid-catalyzed intramolecular oxycyanation of alkenes

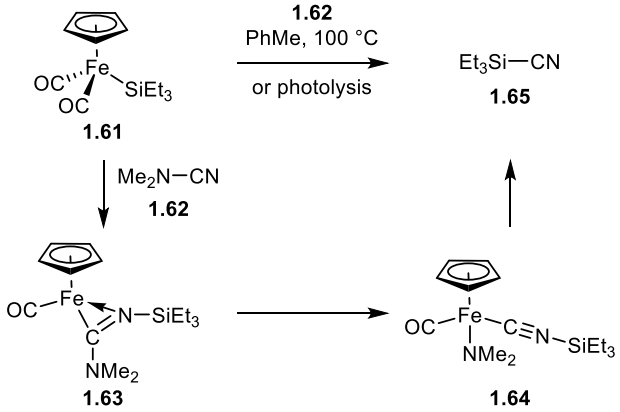
This oxycyanation reaction together with the quinoline-directed oxyacylation reaction published by our group[27] were highlighted by *Angewandte Chemie International Edition*.[28] Both methods featured the activation of traditionally inert C–O σ-bonds and addition of the two groups across tethered alkenes. These methodologies enable the rapid construction of highly functionalized dihydrobenzofurans and chromanes.

### 1.2.3 Aminocyanation

Similar to O–CN bonds, N–CN bonds can be challenging to cleave. As shown in Table 1.1, the bond strengths for the N–CN σ-bond of cyanamides[29] are similar to the C–CN bond of acetonitrile. The N–CN bond length of *N*-(4-chlorophenyl)-*N*-methylcyanamide, as determined by X-ray crystallography, was 1.33 Å.[30] This lies between a typical N–C single bond (1.46–1.48 Å) and a typical N=C double bond (1.35 Å).[23] Additionally, as compared to O–CN σ-bonds, N–CN bonds have an extra

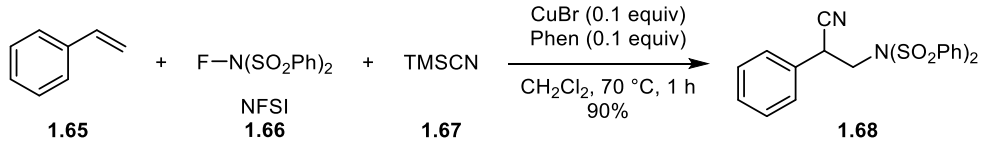
substituent on the nitrogen. The additional steric hindrance from this makes N–CN bond cleavage even more challenging.

The first N–CN bond cleavage by a transition metal was reported in 2009 by Nakazawa et al.[31] This was similar to the mechanism of the O–CN bond cleavage by a molybdenum-silyl complex shown in Scheme 1.11.[25] Cyanamide **1.62** added into iron-silyl complex **1.61** with silyl-migration to give *N*-silyl $\eta^2$-amidino complex **1.63** (Scheme 1.14). N–CN bond cleavage occurs to provide complex **1.64**. Dissociation of triethylsilyl isocyanide and isomerization produces triethylsilyl cyanide.



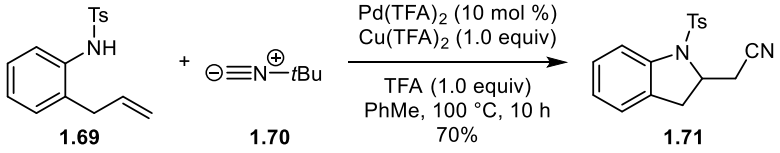

**Scheme 1.14** N–CN bond cleavage by an iron complex

Reports of aminocyanation reactions that result in difunctionalization are rare. In 2013, Xiong, Li, and Zhang et al.[32] reported on the aminocyanation of alkenes. Copper catalysis of styrene (**1.65**) with electrophilic fluorination reagent, *N*-fluorobenzenesulfonimide (NFSI), and trimethylsilylcyanide produced **1.68** in 90% yield (Scheme 1.15). This reaction proceeds by a nitrogen-centered radical addition mechanism, which will not be discussed further.




**Scheme 1.15** Copper-catalyzed intermolecular aminocyanation of alkenes

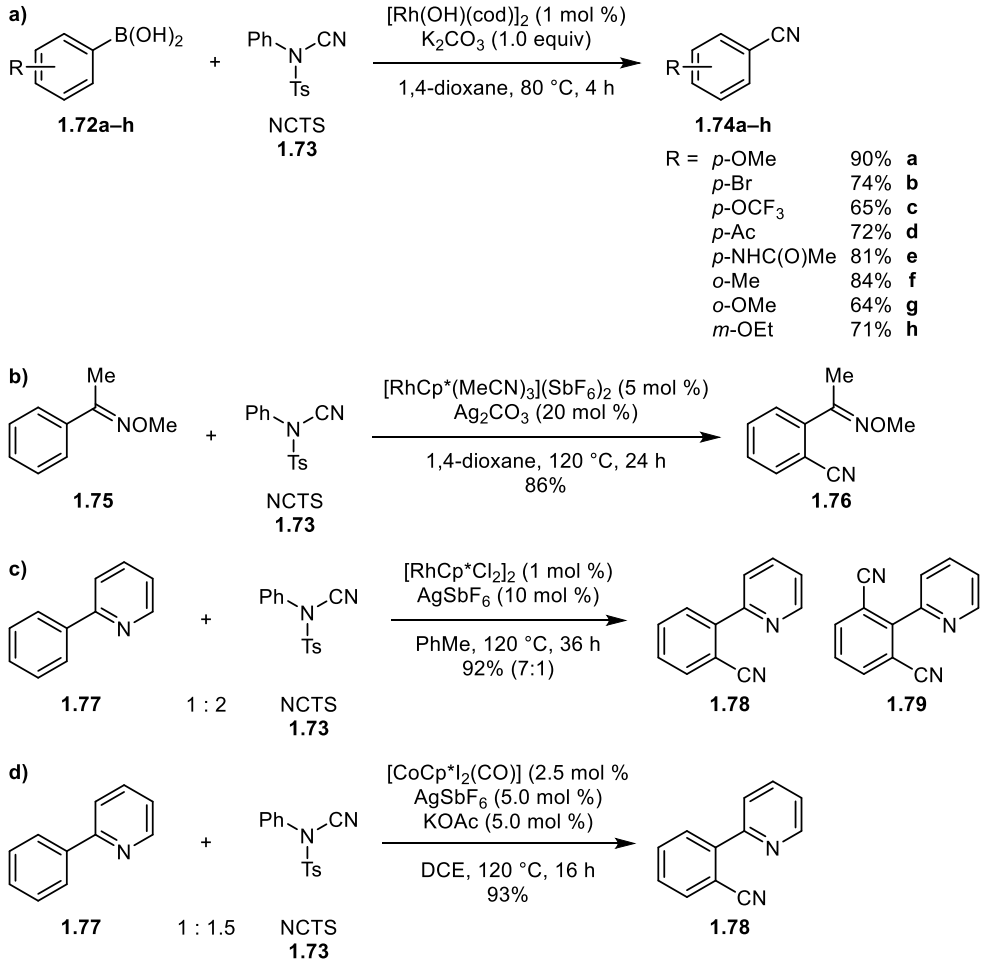
One other aminocyanation reaction was reported by Jiang et al.[33] This used isonitrile **1.70** as the cyanide source. Using palladium-catalysis with $Cu(TFA)_2$ as the stoichiometric oxidant, isonitrile **1.70** inserted into sulfonamide **1.69** producing indoline **1.71** in 70% yield. Anhydrous toluene was used in the reaction; if the toluene was not anhydrous, the nitrile was hydrolyzed or oxidized to an amide.




**Scheme 1.16** Palladium-catalyzed aminocyanation of alkenes with isonitrile as cyanide source

Cyanation has been performed using electrophilic cyanating reagents. Beller et al.[34] reported the electrophilic cyanation of aryl bromides using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) in 2011. While this transformation did not use transition metal-catalysis, it has spawned interest in using NCTS as an electrophilic cyanating reagent in transition metal-catalyzed reactions. These are some of the first examples of catalytic N–CN bond cleavage. NCTS is a bench-stable and less-toxic cyanation reagent. Shortly thereafter, Beller et al.[35] reported the first rhodium-catalyzed cyanation of aryl and alkenyl boronic acids. Under rhodium catalysis, phenylboronic acid **1.72** and NCTS **1.73** reacted, producing benzonitrile **1.74** in 89% yield (Scheme 1.17a). Other cyanation reagents gave only trace amounts of **1.74**. In the absence of potassium carbonate, the reaction was sluggish. Halogenated benzonitrile **1.74b** was readily prepared in good

yields (74%). Electron-donating groups *para*- to the boronic acid tolerated the reaction, generating benzonitrile **1.74a** in 90% yield. Electron-withdrawing groups *para*- to the boronic acid were also tolerated in the reaction, these produced benzonitriles in good yields (**1.74c**, 75%; **1.74d**, 65%). Sterically demanding aryl boronic acids were also effectively cyanated under these conditions (**1.74f**, 84%; **1.74g**, 64%).

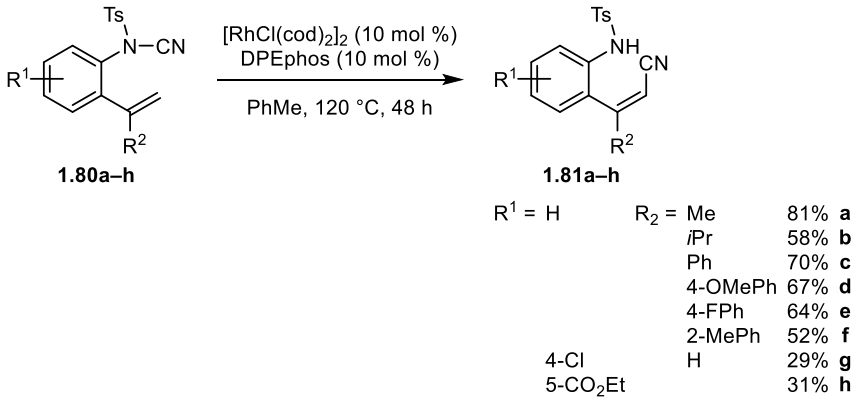



**Scheme 1.17** Aminocyanation reactions using NCTS: a) rhodium-catalyzed; b) with oxime directing group; c) with pyridine directing group; d) cobalt-catalyzed

Other arene cyanations utilizing the N–CN bond cleavage of NCTS (**1.73**) have been developed. Fu et al.[36] reported a rhodium-catalyzed C–H cyanation of arene **1.75**

using NCTS (**1.73**). The rhodium was directed by the *O*-methyl oxime within substrate **1.75** to produce cyanated product **1.76** (Scheme 1.17b). The use of $Ag_2CO_3$ improved the yield. Both rhodium-[37] and cobalt-catalyzed[38] C–H cyanation of arene **1.77** using NCTS (**1.73**) have been reported (Scheme 1.17c–d). These underwent chelation assistance using the internal pyridine as the directing group providing **1.78** in excellent yields (92% and 93%, respectively). Interestingly, the rhodium-catalyzed cyanation produced a 7:1 mixture of **1.78** and **1.79** while the cobalt-catalyzed reaction provided **1.78** as the sole product.

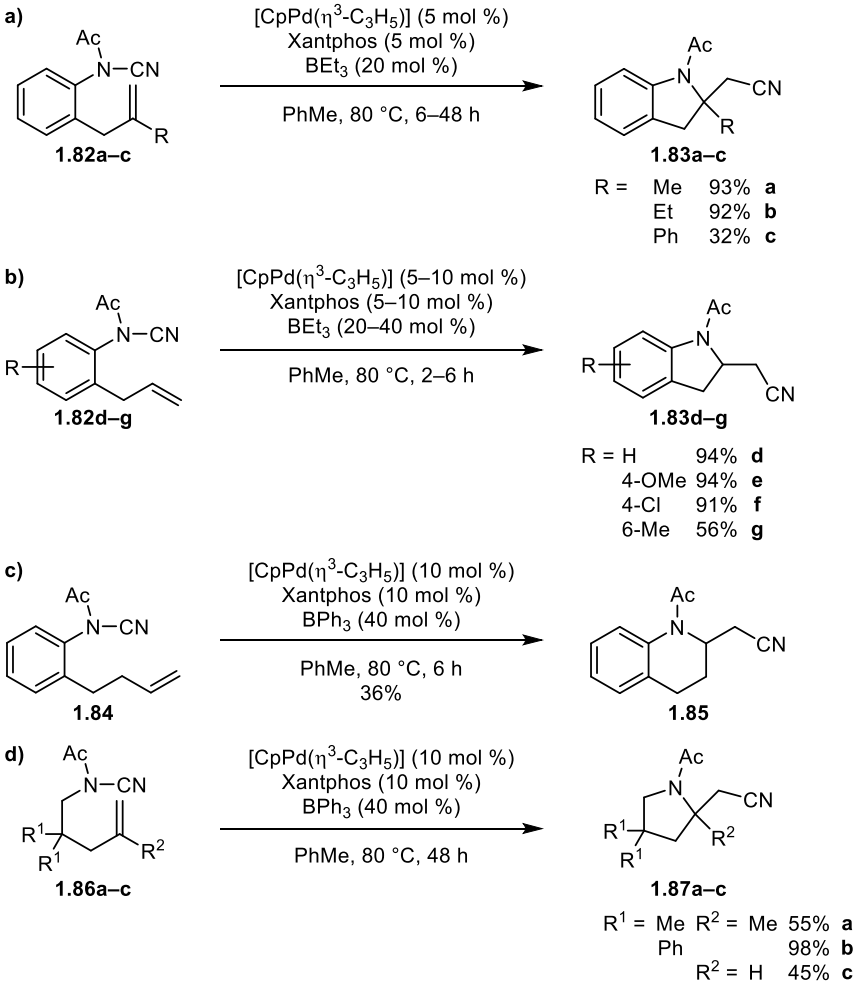
In 2013, Wang and Falck[39] reported the first example of intramolecular cyanation via transition metal-catalyzed N–CN bond cleavage. Heating styrenyl cyanamide **1.80a** with $[RhCl(cod)_2]_2$ (10 mol %) and DPEphos (10 mol %) in toluene at 120 °C for 48 hours generated **1.81a**. This was the first example of atom-economical alkene cyanation. Additionally, an exogenous cyanation reagent was not required. Alkyl substituents α- to the olefin led to acrylonitriles **1.81b–f** in good yields (52–70%). However, a substituent at that position was necessary; substrates without an α-substituent or with a substituent at the β-position failed to generate the acrylonitrile. Electron-deficient arenes resulted in low yields (**1.81g**, 29%; **1.81h**, 31%).




**Scheme 1.18** Rhodium-catalyzed intramolecular β-cyanation of styrenes

Concurrently with our report[5], Nakao et al.[40] reported an intramolecular aminocyanation of alkenes using palladium/Lewis acid catalysis. They were inspired by their own work on oxycyanation.[26] They found that a combination of [CpPd($\eta^3$-$C_3H_5$)] (5 mol %) with Xantphos and $BEt_3$ (40 mol %) allowed the intramolecular aminocyanation of **1.82a** (Scheme 1.19). The alkene inserted into the N–CN bond of the cyanamide moiety in a 5-*exo*-trig fashion. Xantphos was necessary for reactivity; other bisphosphine ligands provided only trace amounts of **1.83a**. [CpPd($\eta^3$-$C_3H_5$)] was the optimal source of palladium(0) as it could undergo reductive elimination of the Cp and allyl groups upon coordination of Xantphos.

The substituent on the alkene could be altered. An ethyl group was tolerated (**1.83b**, 92%); however, when the substituent was a phenyl group, aminocyanation was sluggish (**1.83c**, 32%). Both electron-donating and -withdrawing substituents *para*- to the cyanamide were well tolerated, providing indolines **1.83e** and **1.83f** in 94% and 91% yields, respectively. Cyanamide **1.82g** bearing a methyl group *ortho*- to the cyanamide underwent the aminocyanation reaction albeit in modest yield (56%). The alkene tether could be extended; however, tetrahydroquinoline **1.85** was obtained in only modest yield (36%). Use of triphenylboron as the Lewis acid allowed for the reaction of aliphatic cyanamides **1.86a–c**. These formed pyrrolidines **1.87a–c** in modest to good yields (45–98%).



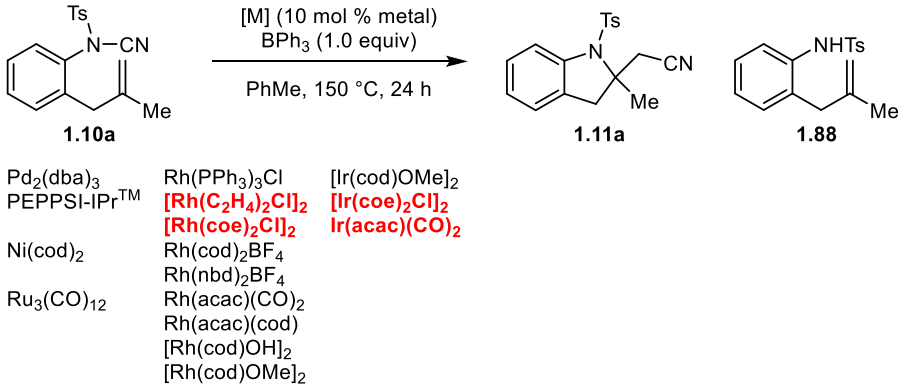

**Scheme 1.19** Palladium/Lewis acid-catalyzed intramolecular aminocyanation of alkenes

## 1.3 Research Proposal

Inspired by the oxycyanation reaction developed by Nakao et al.,[26] our group[1] set out to explore N–CN bond cleavage of an analogous substrate, a cyanamide. Cyanamide **1.10a** was chosen as the test substrate; intramolecular aminocyanation would result in indoline **1.11a**. The nitrogen of the aniline was protected with an *N*-tosyl (tosyl = *p*-toluenesulfonyl) group, which is electron-withdrawing and therefore, should weaken the N–CN bond. Heating cyanamide **1.10a** in toluene under palladium catalysis with added

[1] Initially proposed by Zhongda Pan who also carried out the reaction optimization.

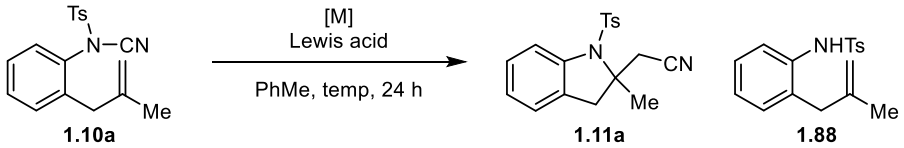
Lewis acid led to incomplete consumption of **1.10a** and did not produce indoline **1.11a**. Instead, sulfonamide **1.88** was observed in all experiments. This indicated that N–CN bond cleavage was indeed possible. Other metal complexes were screened (Rh, Ir, Ni, and Ru) in the reaction (Scheme 1.20). Indoline **1.11a** was identified in the reactions using 10 mol % of $[Rh(C_2H_4)_2Cl]_2$, $[Rh(coe)Cl]_2$, $[Ir(coe)_2Cl_2]_2$, or $Ir(acac)(CO)_2$. Reaction optimization was carried out using $[Rh(C_2H_4)_2Cl]_2$ (5 mol %).




**Scheme 1.20** Identification of aminocyanation product **1.11a** with metal complexes

Reaction of **1.10a** with $[Rh(C_2H_4)_2Cl]_2$ and $BPh_3$ (1.0 equiv) in toluene at 150 °C provided indoline **1.11a** in 40% yield (Table 1.2, entry 1). Decreasing the amount of Lewis acid led to lower reaction efficiency and no observed **1.11a** (entries 2 and 3). Additionally, in the absence of rhodium, **1.11a** was not observed (entry 4). Therefore, both rhodium and Lewis acid were necessary for reactivity. Lowering the temperature improved the yield of indoline **1.11a** (entry 5). Zinc- and lithium-based Lewis acids were ineffective (entries 6–10). Instead, when the more Lewis acidic $B(C_6F_5)_3$[41–42] was used, the yield significantly increased to 70% (entry 11). In the control experiment using $B(C_6F_5)_3$ *in the absence of rhodium*, surprisingly, indoline **1.11a** was produced in a reproducible 90% yield!

**Table 1.2** Optimization of aminocyanation conditions



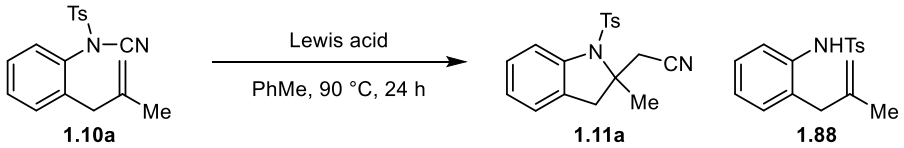

**1.10a** **1.11a** **1.88**

| Entry | Metal | Lewis acid (equiv) | T (°C) | Conversion (%)[a] | Yield of **1.11a** (%)[b] |
|---|---|---|---|---|---|
| 1 | $[Rh(C_2H_4)_2Cl]_2$ | $BPh_3$ (1.0) | 150 | >95 | 40 |
| 2 | $[Rh(C_2H_4)_2Cl]_2$ | $BPh_3$ (0.2) | 150 | 15 | <5 |
| 3 | $[Rh(C_2H_4)_2Cl]_2$ | – | 150 | 17 | <5 |
| 4 | – | $BPh_3$ (1.0) | 150 | 9 | <5 |
| 5 | $[Rh(C_2H_4)_2Cl]_2$ | $BPh_3$ (1.0) | 110 | 86 | 47 |
| 6 | $[Rh(C_2H_4)_2Cl]_2$ | $ZnCl_2$ (1.0) | 110 | 16 | <5 |
| 7 | $[Rh(C_2H_4)_2Cl]_2$ | $ZnBr_2$ (1.0) | 110 | 22 | <5 |
| 8 | $[Rh(C_2H_4)_2Cl]_2$ | $Zn(OTf)_2$ (1.0) | 110 | 8 | <5 |
| 9 | $[Rh(C_2H_4)_2Cl]_2$ | $LiBF_4$ (1.0) | 110 | 8 | <5 |
| 10 | $[Rh(C_2H_4)_2Cl]_2$ | LiCl (1.0) | 110 | 8 | <5 |
| 11 | $[Rh(C_2H_4)_2Cl]_2$ | $B(C_6F_5)_3$ (1.0) | 90 | >95 | 72[c] |
| 12 | – | $B(C_6F_5)_3$ (1.0) | 90 | >95 | 90[c] |

[a] Estimated by $^1$H NMR analysis of the crude product mixture. [b] Determined by $^1$H NMR analysis using *p*-methoxyacetophenone as the internal standard. [c] Yields after column chromatography.

Other Lewis acids were tested under these metal-free conditions. Isoelectronic Lewis acids ($BF_3$•$OEt_2$, $AlCl_3$, and $Me_2AlCl$) also promoted the aminocyanation reaction albeit less efficiently than $B(C_6F_5)_3$ (Table 1.3, entries 1–3). Another strong Lewis acid, $SnCl_4$, also promoted the reaction (entry 4). However, other Lewis acids (AgOTf, $Cu(OTf)_2$, $Zn(OTf)_2$, and $Sc(OTf)_3$) either showed no reactivity or led to decomposition of **1.10a** (entries 5–8). Finally, $BPh_3$ alone was unable to promote the reaction even when heated at 50 °C (entry 9).

**Table 1.3** Lewis acid screening for metal-free aminocyanation




**1.10a** **1.11a** **1.88**

| Entry | Lewis acid (equiv) | T (°C) | Conversion (%)[a] | Yield of **1.11a** (%)[b] |
|---|---|---|---|---|
| 1 | $BF_3$•$OEt_2$ (1.0) | 90 | >95 | 31[c] |
| 2 | $AlCl_3$ (1.0) | 90 | >95 | 52[c] |
| 3 | $Me_2AlCl$ (1.0) | 90 | 57 | 11 |
| 4 | $SnCl_4$ (1.0) | 90 | >95 | 49 |
| 5 | AgOTf (1.0) | 90 | –[d] | <5 |
| 6 | $Cu(OTf)_2$ (1.0) | 90 | –[d] | <5 |
| 7 | $Zn(OTf)_2$ (1.0) | 90 | –[e] | <5 |
| 8 | $Sc(OTf)_3$ (1.0) | 90 | –[e] | <5 |
| 9 | $BPh_3$ | 150 | –[e] | <5 |

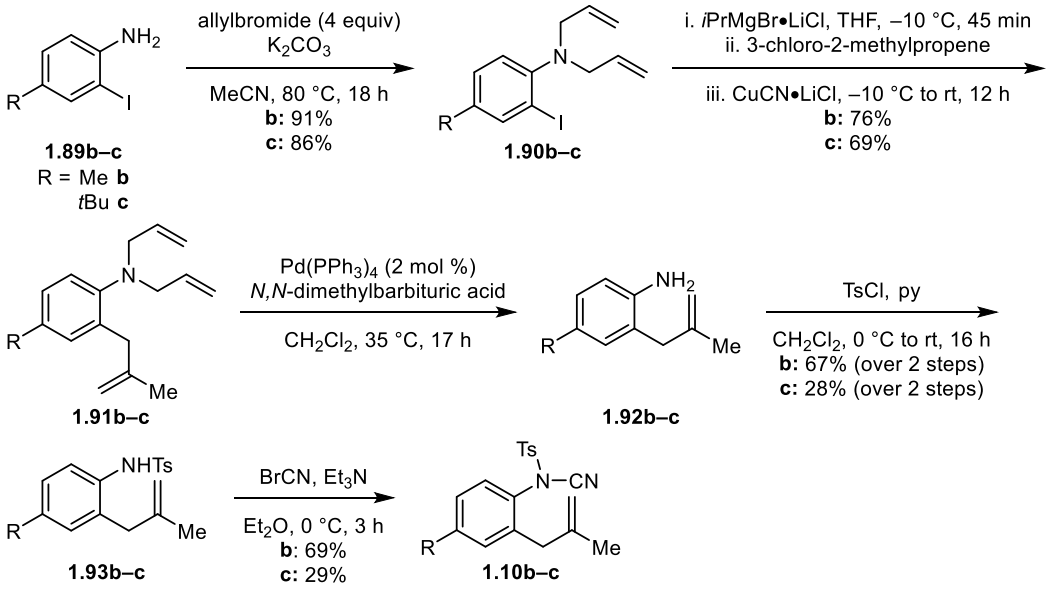
[a] Estimated by $^1$H NMR analysis of the crude product mixture. [b] Determined by $^1$H NMR analysis using *p*-methoxyacetophenone as the internal standard. [c] Yields after column chromatography. [d] No **1.11a** detected by $^1$H NMR, complex mixture formed. [e] No **1.11a** detected by $^1$H NMR, only **1.88** was detected.

### 1.4 Substrate Scope and Limitations

A number of cyanamides were prepared and tested in the Lewis acid-promoted aminocyanation reaction.[2] However, each of these substrates had to be prepared by multi-step synthesis. Cyanamides **1.10b** and **1.10c** were prepared from the corresponding 2-iodoanilines **1.89b** and **1.89c**. Diallylation of 2-iodoanilines **1.89b** and **1.89c** with allylbromide and potassium carbonate produced **1.90b** and **1.90c** in 91% and 86% yield, respectively. Grignard-exchange of the C–I bond with subsequent allylation with 3-

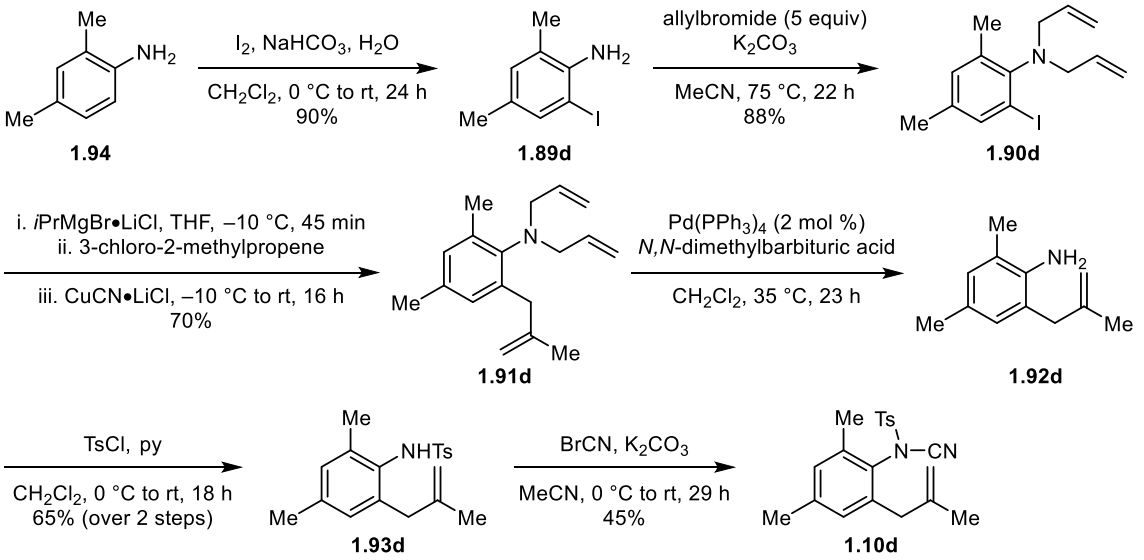
[2] Some of the experiments discussed in this section were performed by Zhongda Pan and Dr. Naveen Rondla.

chloro-2-methylpropene generated anilines **1.91b** and **1.91c** in 76% and 69% yield, respectively. The anilines were deallylated using catalytic $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid. Resulting unpurified anilines **1.92b** and **1.92c** underwent *N*-tosylation in 67% and 28% yields, respectively, over the two steps. *N*-cyanation with cyanogen bromide and triethylamine produced cyanamides **1.10b** and **1.10c** in 69% and 29% yield, respectively.




**Scheme 1.21** Synthesis of cyanamides **1.10b** and **1.10c**

Cyanamide **1.10d** was prepared from 2,4-dimethylaniline **1.94**. Iodination using iodine, sodium bicarbonate, and water generated 2-iodo-aniline **1.89d** in 90% yield. From here, the synthesis of **1.10d** matched that of **1.10b** and **1.10c**. Diallylation produced **1.90d** in 88% yield. Grignard-exchange and alkylation with 3-chloro-2-methylpropene resulted in **1.91d** in 70% yield. Deallylation and *N*-tosylation generated sulfonamide **1.93d** in 65% yield over the two steps. *N*-cyanation with cyanogen bromide and potassium carbonate produced cyanamide **1.10d** in 45% yield.




**Scheme 1.22** Synthesis of cyanamide **1.10d**

It was of interest to prepare cyanamide **1.95** to test the effect of the nitrogen-tethered alkene in the Lewis acid-promoted aminocyanation reaction (Figure 1.1). The synthesis of **1.95** was planned to involve alkylation and methylation of 2-nitroaniline, reduction of the nitro group, *N*-tosylation and *N*-cyanation. 2-Nitroaniline **1.96** underwent alkylation with α-bromomethylstyrene by deprotonation with sodium hydride in DMF then addition of the bromide. Aniline **1.97** was produced in 55% yield. Methylation was attempted using a similar procedure. The aniline was deprotonated with sodium hydride then reacted with methyl iodide for 15 hours. However, the expected product was not obtained. Instead benzimidazole **1.98** was isolated in 46% yield. The structure of **1.98** was determined by spectroscopic experiments.

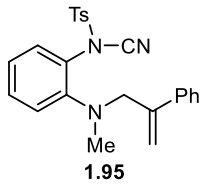
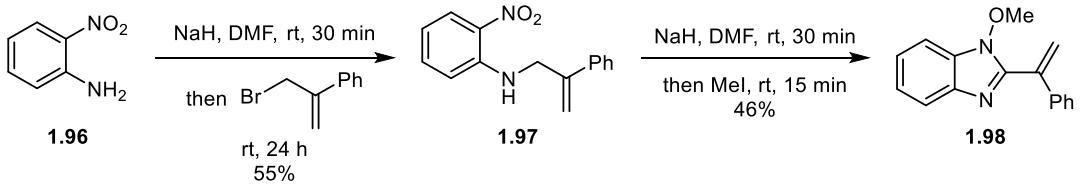
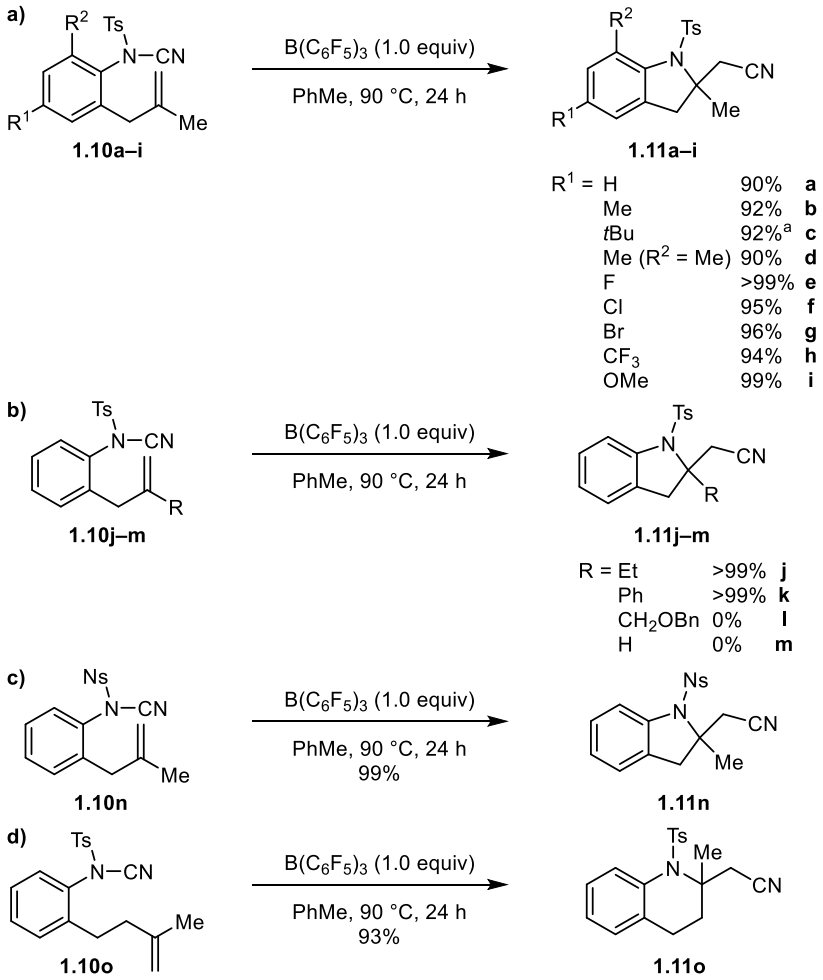



**Figure 1.1** Cyanamide with nitrogen-tethered alkene



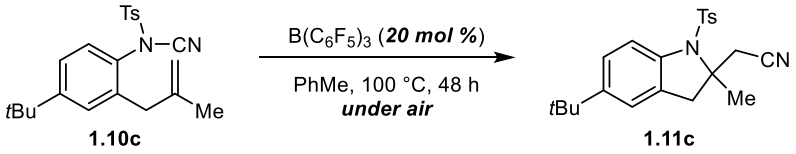

**Scheme 1.23** Attempted synthesis of **1.95** and formation of benzimidazole **1.98**

The cyanamide substrates **1.10a–o** were tested in the Lewis acid-promoted aminocyanation by reacting with 1.0 equivalent of $B(C_6F_5)_3$ in toluene at 90 °C for 24 hours. Alkyl-substituted cyanamides **1.10b–d** produced indolines **1.11b–d** in excellent yields (Scheme 1.24a). Methyl-substituted indoline **1.11b** was isolated in 92% yield; *tert*-butyl indoline **1.11c** was isolated in 92% yield (average of two reactions). A methyl-substituent *ortho*- to the cyanamide was well tolerated, affording **1.11d** in 90% yield. Halogen-substituents *para*- to the cyanamide were also well tolerated, providing indolines **1.11e–g** in excellent yields (95–99%). Both electron-withdrawing and electron-donating substituents *para*- to the cyanamide were well tolerated, affording indolines **1.11h** and **1.11i** in 94% and 99% yields, respectively. Ethyl- and phenyl-substituted alkenes **1.10j–k** underwent the reaction smoothly, affording indolines **1.11j** and **1.11k** in >99% yield each. However, introduction of a benzyloxy substituent α- to the alkene (**1.10l**) completely inhibited the reaction, presumably due to the inductive effect of C–O bonds. Additionally, mono-substituted alkene **1.10m** was completely unreactive under the reaction conditions. Cyanamide **1.10n** bearing a *p*-nosyl-protecting group underwent the reaction to produce indoline **1.11n** in near quantitative yield. As nosyl groups can be removed under relatively mild conditions,[43] this would allow for further functionalization of the nitrogen atom. Cyanamide **1.10o** with an extended alkene tether afforded tetrahydroquinoline **1.11o** in 93% yield.




**Scheme 1.24** Scope of Lewis acid-promoted alkene aminocyanation: a) substituents at aromatic ring; b) substituents at olefin; c) Ns protecting group; d) extended tether

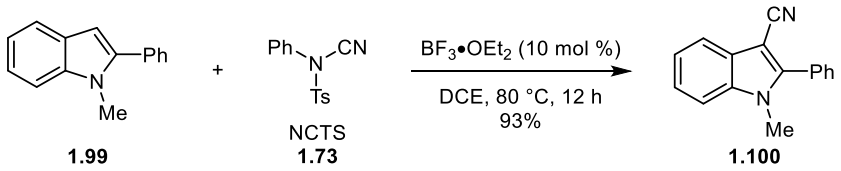
Heating cyanamide **1.10c** with catalytic $B(C_6F_5)_3$ (20 mol %) in toluene at 100 °C for 48 hours afforded indoline **1.11c** in 94% yield (Scheme 1.25). This reaction was carried out on 2.0 mmol scale instead of the usual 0.1 mmol scale. Additionally, the reaction was prepared under air instead of in the air-free glovebox. Overall, this one reaction showed that the Lewis acid-catalyzed aminocyanation of alkenes could be made catalytic, conducted on larger scale, and was tolerant of air.




**Scheme 1.25** Lewis acid-catalyzed alkene aminocyanation under air

## 1.5 Mechanistic considerations

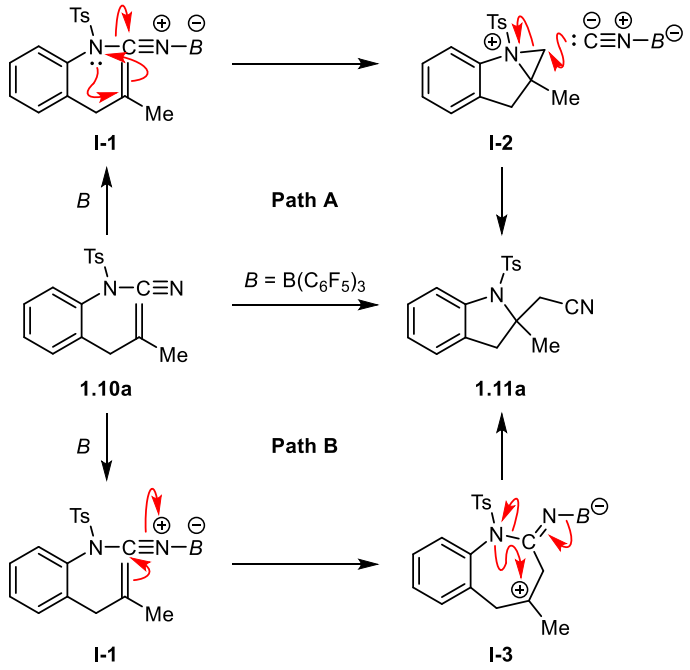
Because the Lewis acid-promoted aminocyanation reaction did not involve the use of transition metals, we needed to find an alternative mechanistic hypothesis. Precedence for Lewis acid-promoted cyanation had been reported by Wang et al.[44] They had performed the cyanation of indoles (**1.99**) and pyrroles with NCTS (**1.73**) as the electrophilic cyanide source. The reaction was promoted by catalytic $BF_3$•$OEt_2$. While this example provides precedence for N–CN σ-bond cleavage under Lewis acidic conditions, only the cyano group was added. For our system, both the cyano group and the sulfonamide added across an alkene.




**Scheme 1.26** Cyanation of indole **1.99** using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide

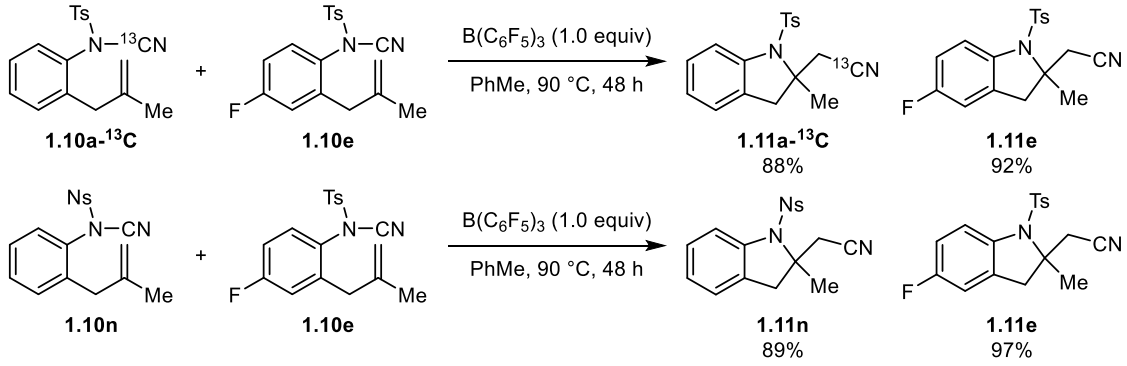
We initially proposed two possible paths for our intramolecular aminocyanation of alkenes. First, the cyanamide moiety of **1.10a** coordinated to the Lewis acid affording adduct **I-1**. Nucleophilic attack by the nitrogen at the alkene and back attack by the alkene with dissociation of the nitrile would generate aziridinium ion **I-2** (Path A). The dissociation of the nitrile seemed feasible due to the known atom abstracting properties of $B(C_6F_5)_3$.[40–41] Alternatively, the alkene could attack the central carbon of the cyanamide, the typical site for nucleophilic attack on cyanamides (Path B). This would generate the

seven-membered benzazepine-type intermediate **I-3**. Collapse of this intermediate would afford **1.11a**. Path B was consistent with the success of substrates **1.10j** and **1.10k**, which had more nucleophilic alkenes, and with the failure of substrates **1.10l** and **1.10m**, which were less nucleophilic.



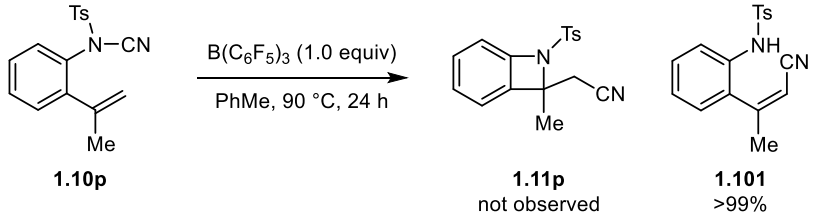

**Scheme 1.27** Proposed mechanism

A double-crossover experiment was conducted by heating a mixture of $^{13}$C-labeled cyanamide **1.10a-$^{13}$C** and **1.10e** with $B(C_6H_5)_3$ in toluene at 90 °C for 48 h. The only products generated were non-crossover products **1.11a-$^{13}$C** and **1.11e** in 88% and 92% yields, respectively. Furthermore, the double-crossover experiment between Ns-protected cyanamide **1.10n** and **1.10e** afforded only the non-crossover products **1.11n** and **1.11e** in 89% and 97% yields, respectively. Because crossover was not detected, Path A was ruled out as a potential mechanism.

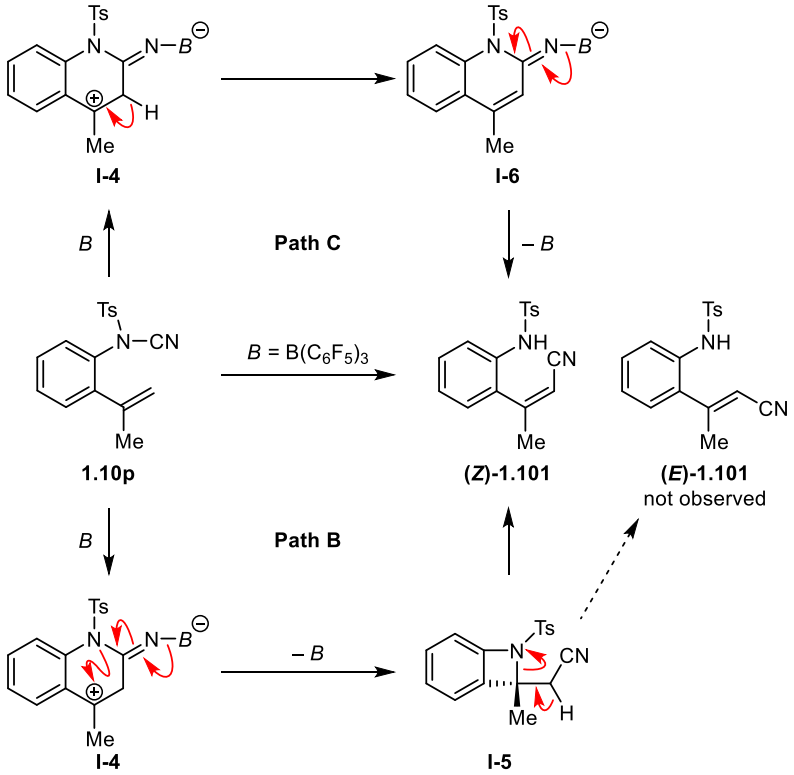



**Scheme 1.28** Double-crossover experiments

Subjection of cyanamide **1.10p** to the aminocyanation conditions did not afford the corresponding four-membered product **1.11p**. Instead it resulted in (*Z*)-alkenyl nitrile **1.101** in quantitative yield (Scheme 1.29). If Path B were operative as the aminocyanation mechanism, nucleophilic addition of the alkene to the cyanamide carbon would lead to six-membered intermediate **I-4**. This would collapse to the strained benzazetidine intermediate **I-5** (Scheme 1.30, Path B), which could undergo elimination to the alkenyl nitrile. However, this path would not account for the observed regioselectivity; if it were operative, both alkenyl cyanides (*Z*)-**1.101** and (*E*)-**1.101** should be generated. Instead, it appeared that **I-4** underwent elimination to **I-6** followed by ring-opening (Scheme 1.30, Path C).




**Scheme 1.29** Formation of alkenyl nitrile **1.101**

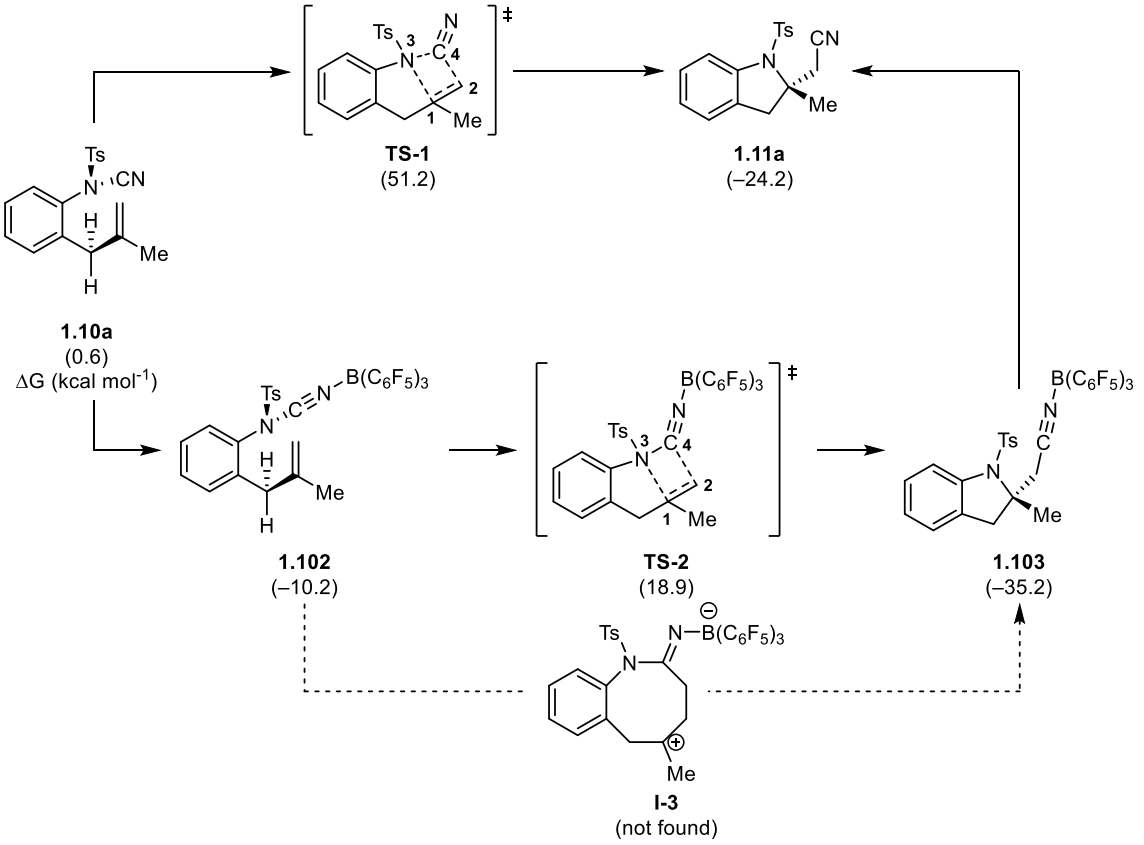



**Scheme 1.30** Mechanistic proposal for selective formation of alkenyl nitrile **1.101**

Cyanamide **1.10p** was one of the substrates studied in the rhodium-catalyzed cyanation of α-methyl styrenes by Wang and Falck.[39] The product they obtained after reacting with NCTS (**1.73**) was identical to **1.101**. This implies that the cyano-transfer reaction developed by Wang and Falck did not require rhodium. However, when they had tested the reactivity in the absence of rhodium only unconsumed starting material was recovered. Additionally, multiple catalysts promoted the reaction including other rhodium and palladium complexes with or without added phosphine ligand. However, the mechanism of the rhodium-catalyzed cyanation was not studied, so it remains possible that the metal was not involved in direct oxidative addition of the N–CN bond but may have acted as a Lewis acid promoter.

In 2015, Li et al.[45] reported on the application of DFT calculations to our system, offering new insights into the mechanism. All attempts to locate proposed seven-

membered intermediate **I-3** were unsuccessful. Instead, the alkene addition step occurred in a concerted and asynchronous fashion. The formation of the C2–C4 bond and the cleavage of the N3–C4 bond occurred simultaneously. However, these occurred prior to the formation of the C1–N3 bond. This concerted asynchronous alkene addition was unprecedented as other electrophilic alkene additions (e.g. hydroboration of alkenes) proceed in a concerted synchronous fashion.

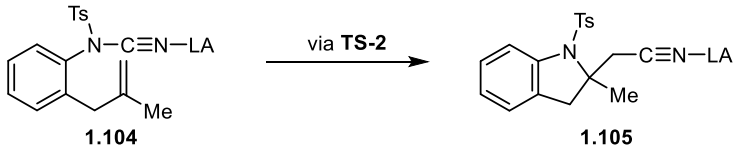



**Scheme 1.31** Mechanistic proposal of aminocyanation from theoretical study

In the absence of $B(C_6F_5)_3$, alkene addition to the cyanamide **1.10a** occurred through cyclic transition state **TS-1**. This had a formidable free energy (51.2 kcal $mol^{-1}$). When $B(C_6F_5)_3$ was present, coordination to the cyano group led to adduct **1.102**. This proceeded through cyclic transition state **TS-2** to provide adduct **1.103**, which generated

**1.11a** upon dissociation of $B(C_6F_5)_3$. The free-energy barrier for this path (29.1 kcal $mol^{-1}$) was much lower than the un-catalyzed path. Additionally, the strength of the Lewis acid directly correlated to the free energy barrier of the cyclization. Weaker Lewis acids ($SnCl_4$ and $BPh_3$) had higher free energy barriers for alkene addition (Table 1.4). The experimentally-determined yields matched this trend. Overall, a strong Lewis acid was critical for the transformation.

**Table 1.4** Correlation of Lewis acid strength and aminocyanation result




**1.104** **1.105**

| Lewis acid | Lewis acidity[a] | Calculated free energy barrier (kcal $mol^{-1}$) | Experimental yield of **1.11a** |
|---|---|---|---|
| $B(C_6F_5)_3$ | strongest | 29.1 | 90% |
| $SnCl_4$ | | 32.7 | 49% |
| $BPh_3$ | weakest | 36.8 | 0% |

[a] Calculated based on the corresponding hydride affinity. $B(C_6F_5)_3$: –91.6 kcal $mol^{-1}$; $SnCl_4$: –123.3 kcal $mol^{-1}$; $BPh_3$: –130 kcal $mol^{-1}$.

## 1.6 Concluding Remarks

We serendipitously discovered a Lewis acid-promoted aminocyanation reaction where the N–CN bond of a cyanamide is cleaved and added across a pendant alkene. This enabled rapid construction of indolines and tetrahydroquinolines in excellent yields. Preliminary mechanistic experiments suggested that the cyclization occurs in an intramolecular fashion and that the cyano group remains bound throughout the reaction. Additionally, recent computations suggested that the alkene addition occurs in a novel concerted asynchronous step. Further work in our group has focused on developing a transition metal-catalyzed aminocyanation reaction.

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# Part II: Progress Toward a Total Synthesis of Drimentine C

# Chapter 2: Introduction to the Drimentine Alkaloids

## 2.1 Introduction

A continued need exists to discover and develop new antibiotics due to the development of multidrug resistant bacteria. In the past, natural products isolated from microorganisms were the source of most antibiotics on the market. However, there has been a decrease in antibiotics research and in the screening of natural products over the past decades, which has led to a scarcity of new antibiotic classes.[1–5] Part of this decrease in screening is due to the increasing re-isolation of known natural products from new sources. At this point, most newly isolated natural products are only minimally screened for cytotoxic activity leading to natural products without obvious overt toxicity being classified as inactive. Yet, these inactive natural products must have some inherent activity; simply, their activities have not yet been discovered.[6] Therefore, when a novel family of natural products is discovered, it should be broadly screened in order to find rare activities or unanticipated modes of action.

Part Two of this Thesis will describe efforts toward the total synthesis of drimentine C, one of a small alkaloid family that are of interest for further study to determine their targets and modes of action. This chapter is an introduction to the drimentine family.

## 2.2 Isolation, Biological Activity, and Structural Elucidation of the Drimentines

In 1998, Lacey et al.[7] filed a patent on a novel family of alkaloids. Drimentines A–E (**2.1**–**2.5**, Figure 2.1a) were isolated from the mycelia of *Actinomycete* strain MST-8651, which was obtained from soil found under an *Acacia* sp. tree in a dry creek bed near Dungog, New South Wales, Australia. Also isolated was piericidin A (**2.7**, Figure 2.1b), a potent inhibitor of NADH-ubiquinone reductase, one of the mitochondrial

electron transport chain proteins.[8–10] Lacey et al.[7] prepared 3,25-dihydrodrimentine E (**2.6**) by treatment of **2.5** with 10% palladium/charcoal for 1.5 hours.

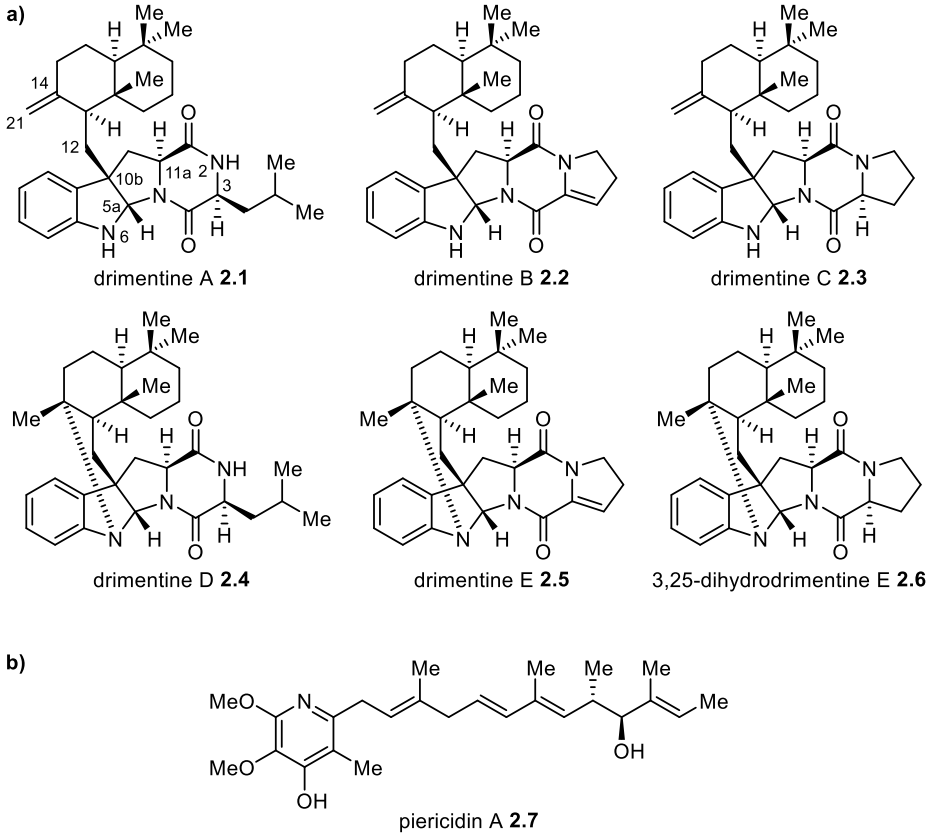



**Figure 2.1** Secondary metabolites isolated from *Actinomycete* strain MST-8651: a) drimentines A–E (**2.1**–**2.5**) and 3,25-dihydrodrimentine E (**2.6**); b) piericidin A (**2.7**)

No further reports on the drimentines appeared until 2012 when Li and coworkers[11–12] reported the isolation of two additional drimentines (**2.8**–**2.9**, Figure 2.2a) together with structurally-related indotertine A (**2.12**). These were isolated from *Streptomyces* sp. CHQ-64, which was obtained from reeds rhizosphere soil collected from the mangrove conservation area in Guangdong, China. *Streptomyces* sp. CHQ-64 had been chosen for metabolite screening out of 103 marine-derived *Actinomycetes*

because of its cytotoxicity against P388, a multidrug resistant murine leukemia cell line, and its interesting HPLC profile of secondary metabolites. Additional screening of *Streptomyces* sp. CHQ-64 led to the isolation of drimentine H (**2.10**) and indotertine B (**2.13**) with re-isolation of **2.3** in 2013[13] and drimentine I (**2.11**) in 2016.[14] Li et al.[15] have continued investigating the secondary metabolites of *Streptomyces* sp. CHQ-64. Genome scanning revealed a partial gene cluster likely encoding for the biosynthesis of polyene-polyol compounds. This led to the isolation of six new polyene-polyol macrolides, reedsmycins A–F (**2.14**–**2.15**, Figure 2.2b), that exhibit promising antifungal activity against *Candida albicans*.

Initial *in vitro* biological assays demonstrated that the drimentines possess weak antitumor and antibacterial activities. In terms of antitumor activity, drimentines B–E (**2.2**–**2.5**) displayed weak activity against NS-1 murine myeloma cells ($IC_{50}$ = 11–71 μg/mL‡).[7] Drimentine G (**2.9**) displayed moderate cytotoxic activity against four human cancer cell lines: colon carcinoma HCT-8, liver hepatocellular carcinoma Bel-7402, alveolar adenocarcinoma A549, and ovarian cancer A2780 ($IC_{50}$ = 2.81, 1.38, 1.01, and 2.54 μM, respectively).[11] Due to this activity, Li et al.[16] filed a patent for **2.9** in 2011. Drimentines F and H (**2.8**, **2.10**) showed no activity against the tested cell lines, leading Li et al.[13] to hypothesize that "the exchangeable NH-proton in the diketopiperazine seems essential to the cytotoxic activity." In an attempt to identify its molecular target, drimentine G (**2.9**) was assayed against topoisomerase I, topoisomerase II, and Hsp90 and was found to have weak inhibitory activity against topoisomerase I.[11] In terms of antibacterial activity, drimentine E (**2.5**) was found to inhibit the growth of *Bacillus subtilis* down to 50 μg/mL.[7]

‡ Calculated from reported inhibition data.

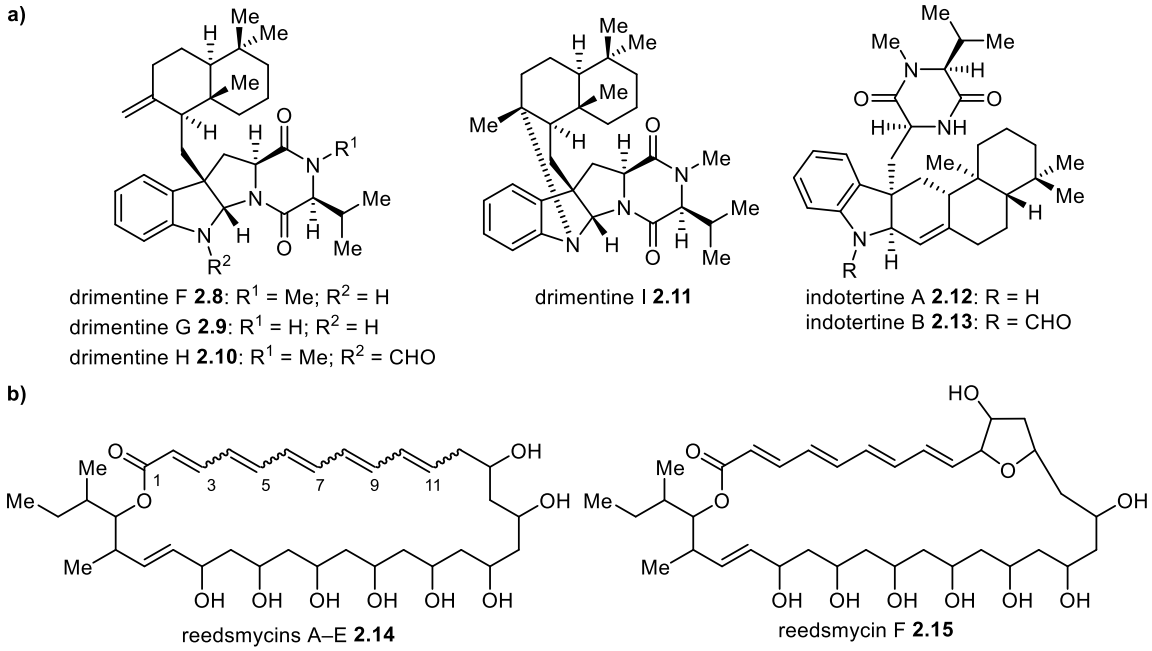



**Figure 2.2** Secondary metabolites isolated from Streptomyces sp. CHQ-64: a) drimentines F–I (**2.8**–**2.11**) and indotertines A–B (**2.12**–**2.13**); b) reedsmycins A–F (**2.14**–**2.15**)

The structures of drimentines A–I (**2.1**–**2.5**, **2.8**–**2.13**) were initially elucidated by a combination of spectroscopic methods. Their relative configurations were determined from nOe experiments. Absolute configurations were deduced by comparison of time-dependent density functional theory (TDDFT) electronic circular dichroism (ECD) spectra calculated for the solution conformers with the experimental solution CD spectra. This protocol has been found to be a powerful and reliable method for determining the absolute configuration of indole alkaloids.[17–19] Furthermore, X-ray crystallographic analysis of drimentine F (**2.8**) allowed for unambiguous absolute configuration assignment and confirmation of the overall structure.[11]

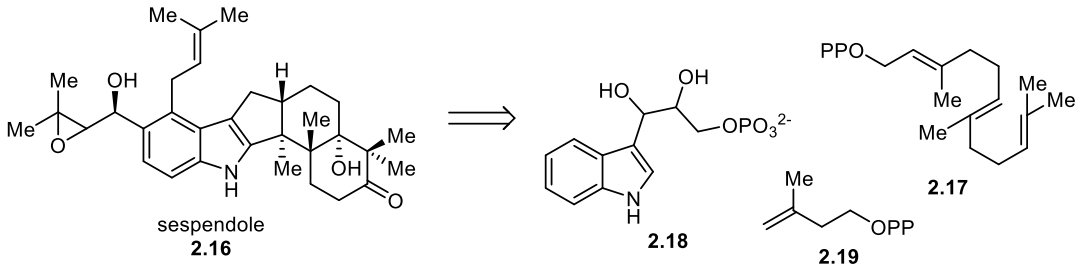
Conserved within the drimentines is a hexahydropyrrolo[2,3-*b*]indole core connected at C10b (see Figure 2.1a, drimentine numbering) through a methylene bridge to a drimane-type sesquiterpene moiety. This pyrroloindoline core is fused to a

diketopiperazine ring. The identity of the amino acid condensed with L-tryptophan in the diketopiperazine provides one key point of difference between the drimentines: L-leucine (**2.1**, **2.4**), 2,3-didehydro- L-proline (**2.2**, **2.5**), L-proline (**2.3**, **2.6**), *N*-methyl-L-valine (**2.8**, **2.10**–**2.11**), and L-valine (**2.9**). Drimentine H **(2.10)** is the only member with formylation at N6. Additionally, four drimentines (**2.4**–**2.6**, **2.11**) are heptacyclic containing an additional σ-bond between N6 and C14. Overall, the drimentines each possess between six and eight stereocenters, two or three of which are all-carbon quaternary stereocenters.

## 2.3 Proposed Biosynthesis of Drimentines

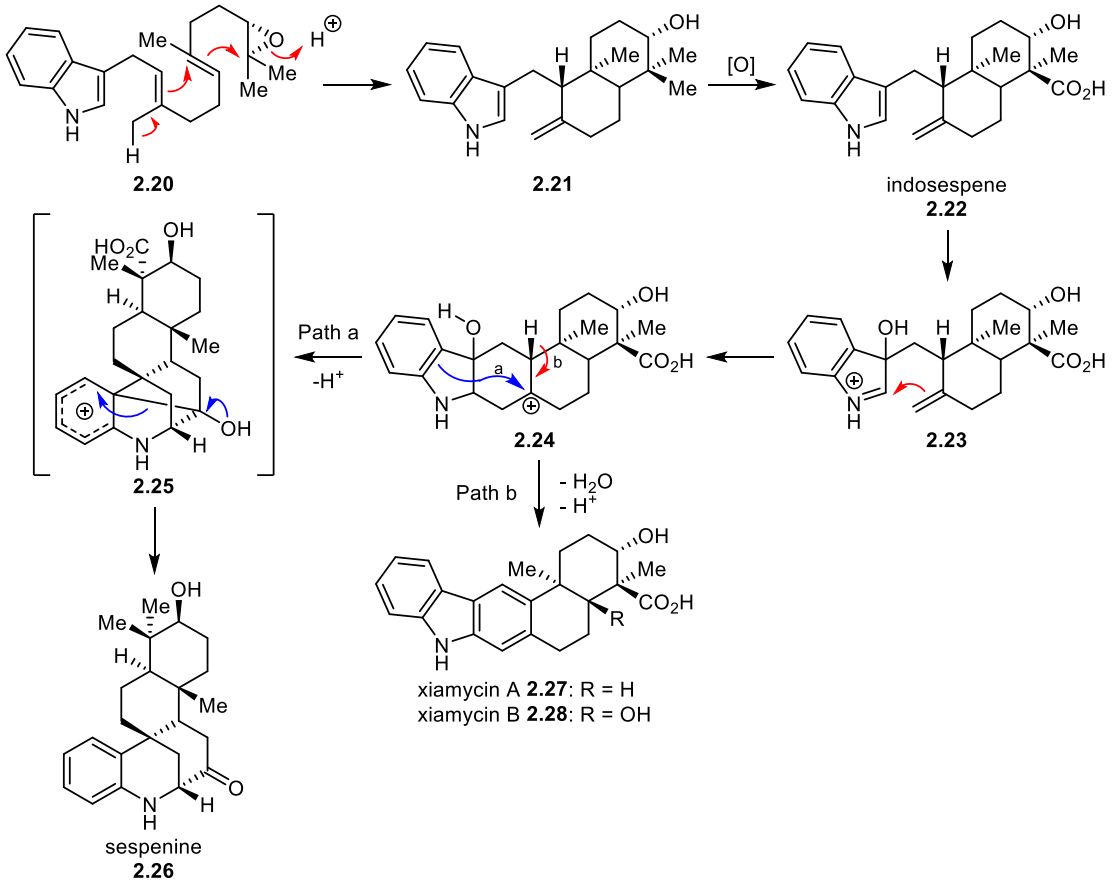
The structure of the drimentines places them within a larger class of indolosesquiterpenes, natural products containing a sesquiterpene unit attached to an indole derivative. These are relatively common metabolites of plants, but are quite rare in microorganisms in general and prokaryotes in particular.[20–21] As such, the proposed biosynthesis of the drimentines and their close relatives, the indotertines, follows closely with that of other indolosesquiterpenes.

Sespendole (**2.16**), the first indolosesquiterpene isolated from a microorganism (*Pseudobotrytis terrestris*, a filamentous fungus), has provided a basis for subsequent biosynthetic proposals of similar natural products. The biosynthesis of **2.16** was studied by feeding experiments using [$^{13}$C]acetate, [$^{13}$C]tryptophan, and [$^{15}$N]anthranilic acid.[22] The sesquiterpene moiety was found to originate from farnesylpyrophosphate **2.17**, which is biosynthesized via the mevalonate pathway. Ultimately, indole-3-glycerol phosphate **2.18**, derived from anthranilic acid and ribose, and **2.17** undergo condensation and cyclization to form the core structure (Scheme 2.1). Two molecules of dimethylallyl pyrophosphate **2.19** are incorporated into the core structure as the side chains.




**Scheme 2.1** Fragments from biosynthesis of sespendole (**2.16**)

The biosynthesis of indosespene (**2.22**), sespenine (**2.26**), and xiamycins A and B (**2.27**–**2.28**), four of the first indolosesquiterpenes isolated from prokaryotes, was reasoned in analogy to **2.16** (Scheme 2.2).[21,23] They originate from 3-farnesylindole precursor **2.20** where the side chain is activated as an epoxide. Cyclization of the side chain to decalin **2.21** and subsequent oxidation provides indosespene (**2.22**). Further oxidation to indolenine **2.23** followed by an iminium-olefin cyclization would result in carbenium ion **2.24**. Trapping of the carbenium ion could occur by either of two paths. In the first path, a π-bond of the electron-rich aromatic ring attacks the tertiary carbocation providing intermediate **2.25**, collapses to pentacyclic sespenine (**2.26**, path a). Alternatively, elimination followed by loss of an equivalent of water and subsequent rearomatization to provide the xiamycins (**2.27**–**2.28**, path b). A similar rearrangement has been proposed for the biosynthesis of aspernomine (**2.30**) from nominine[24] (**2.29**), two fungal indolosesquiterpenes (Figure 2.3).[25–27]




**Scheme 2.2** Proposed biosynthesis of indosespene (**2.22**), sespenine (**2.26**), and xiamycins A and B (**2.27**–**2.28**) from 3-farnesylindole epoxide **2.20**

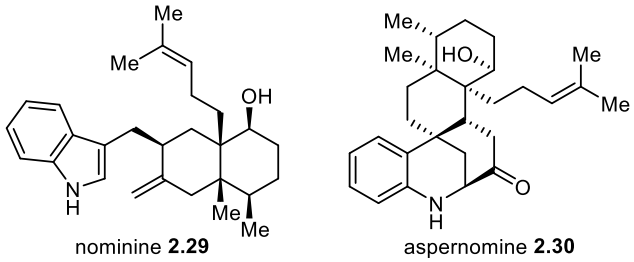
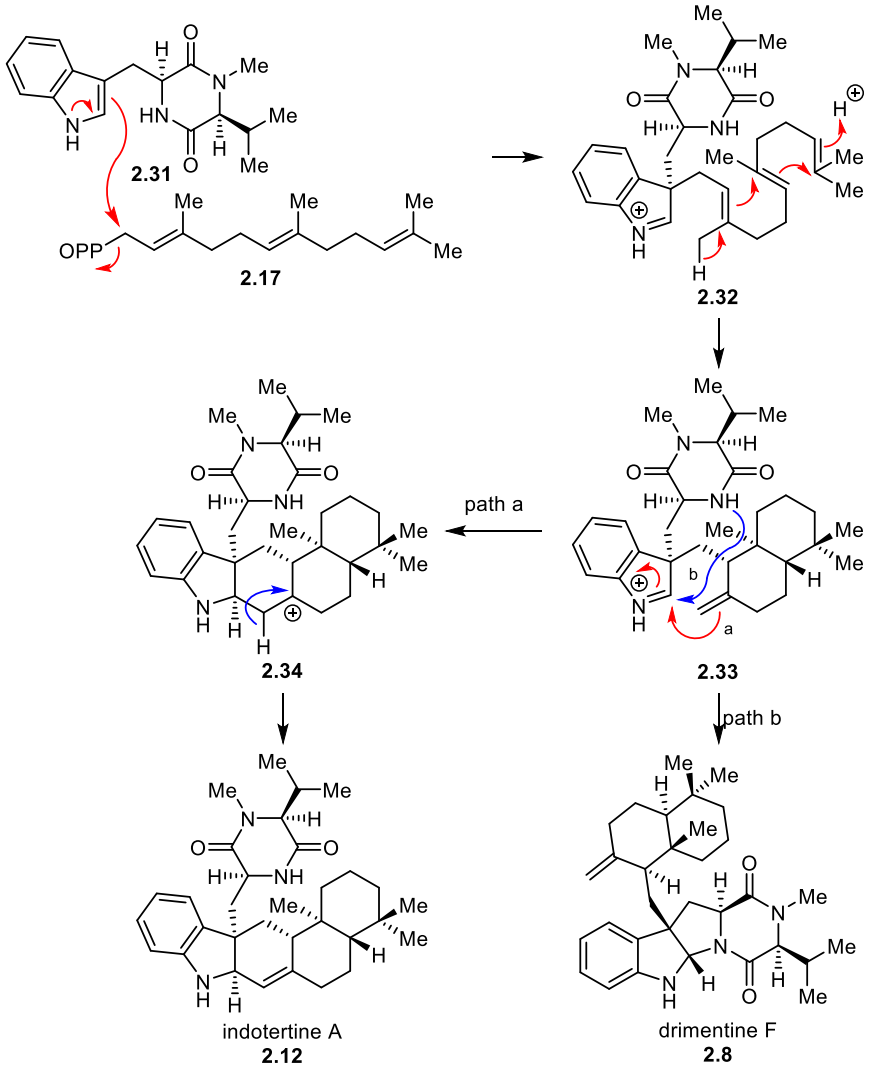



**Figure 2.3** Indolosesquiterpenes: nominine (**2.29**) and aspernomine (**2.30**)

Noting the structural similarities to other indolosesquiterpene natural products, Li et al.[11] proposed an analogous biosynthetic path for the drimentines and indotertines (Scheme 2.3). Diketopiperazine **2.31** would condense onto farnesylpyrophosphate **2.17**, prepared via the classic mevalonate pathway.




**Scheme 2.3** Proposed biosynthesis of drimentines F (2.8) and indotertine A (2.12)

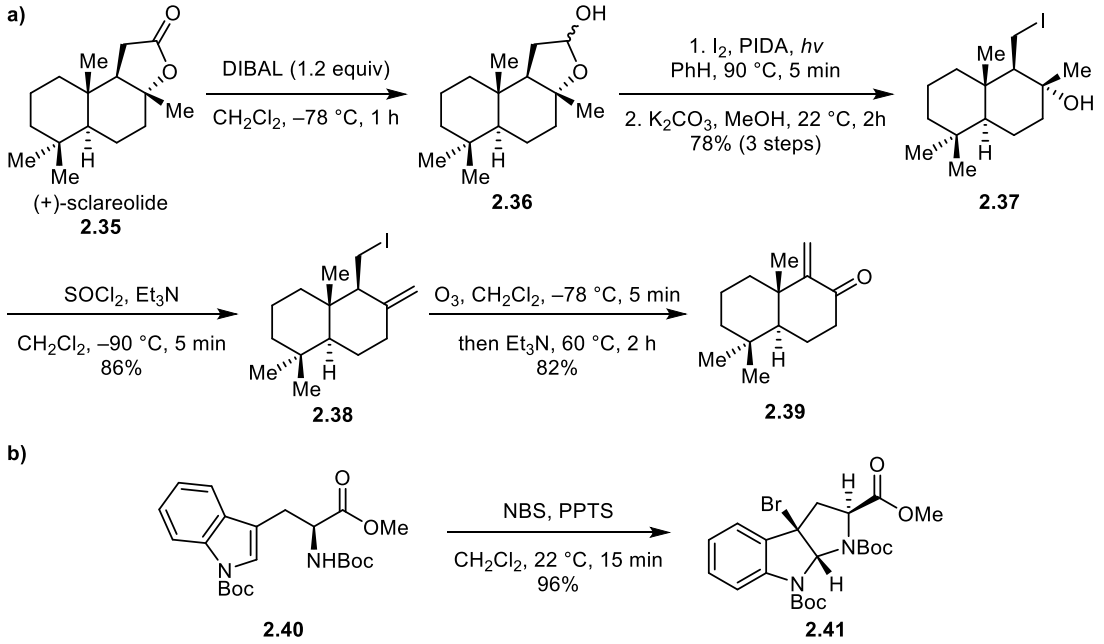
A cationic cascade cyclization of intermediate **2.32** would produce the decalin ring system of intermediate **2.33**. Trapping of the indolenine could take place in two ways. Iminium-olefin cyclization (path a) would result in carbenium ion **2.34**, which could undergo elimination to form indotertine A (**2.12**). Alternatively, nucleophilic addition of an amidic nitrogen in the diketopiperazine ring would result in drimentine F (**2.8**).

## 2.4 Reported Total Syntheses of the Drimentines and Related Compounds

Currently, there is a single report[28] of a collective total synthesis of drimentines A, F, and G and indotertine A in the literature. In a second recent report, a biomimetic route produced non-natural drimentine derivative $\Delta^{8'}$-isodrimentine A.

### 2.4.1 Li's Total Synthesis of Drimentines A, F, and G and Indotertine A

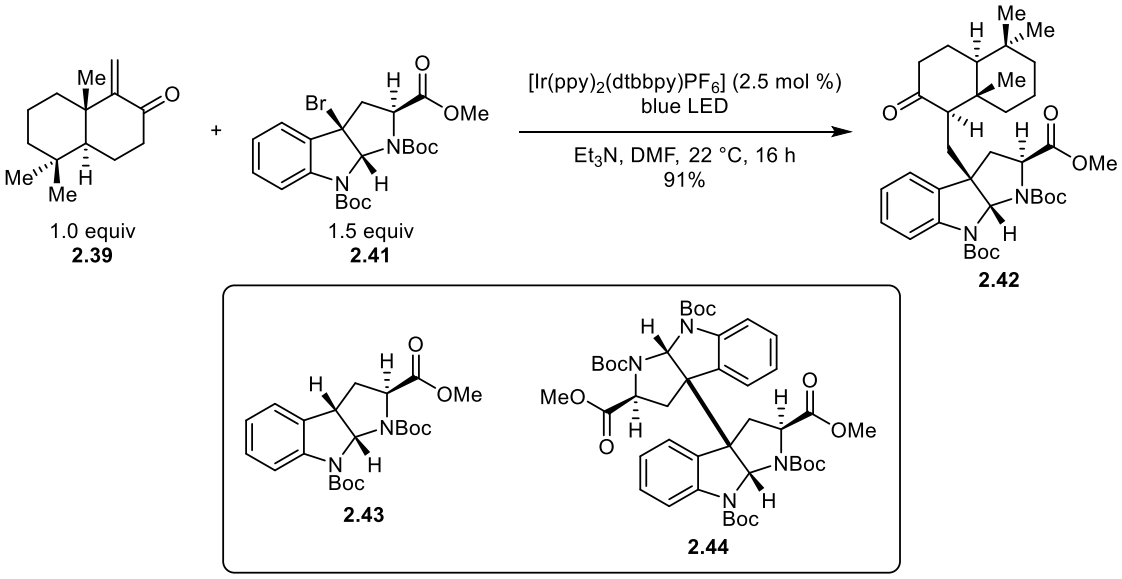
One year after the initial report on the isolation of drimentines F and G (**2.8**–**2.9**) and indotertine A (**2.12**), Li et al.[28] published the first total synthesis of drimentines A, F, and G (**2.1**, **2.8–2.9**) as well as indotertine A (**2.12**). Enone **2.39** was prepared from commercially-available (+)-sclareolide (**2.35**), which was converted to iodide **2.37** using a procedure developed by Baran et al.[29] (Scheme 2.4). DIBAL-mediated reduction of **2.35** produced scleral **2.36**, which underwent hypoiodite-mediated C–C bond cleavage with $I_2$, PIDA, and light. Hydrolysis of the resulting formate group provided iodoalcohol **2.37** in 78% yield over the three steps. Olefin **2.38** was obtained in 86% yield from kinetically-controlled dehydration of **2.37** with thionyl chloride and triethylamine. Ozonolysis of the exocyclic olefin with subsequent β-elimination under basic conditions provided enone **2.39** in 82% yield on multigram scale. Electrophilic bromocyclization of L-tryptophan derivative **2.40** with *N*-bromosuccinimide (NBS) and catalytic pyridinium *p*-toluenesulfonate (PPTS) provided coupling partner **2.41** in 96% yield on decagram scale.




**Scheme 2.4** Preparation of key intermediates: a) enone **2.39**; b) bromopyrroloindoline **2.41**

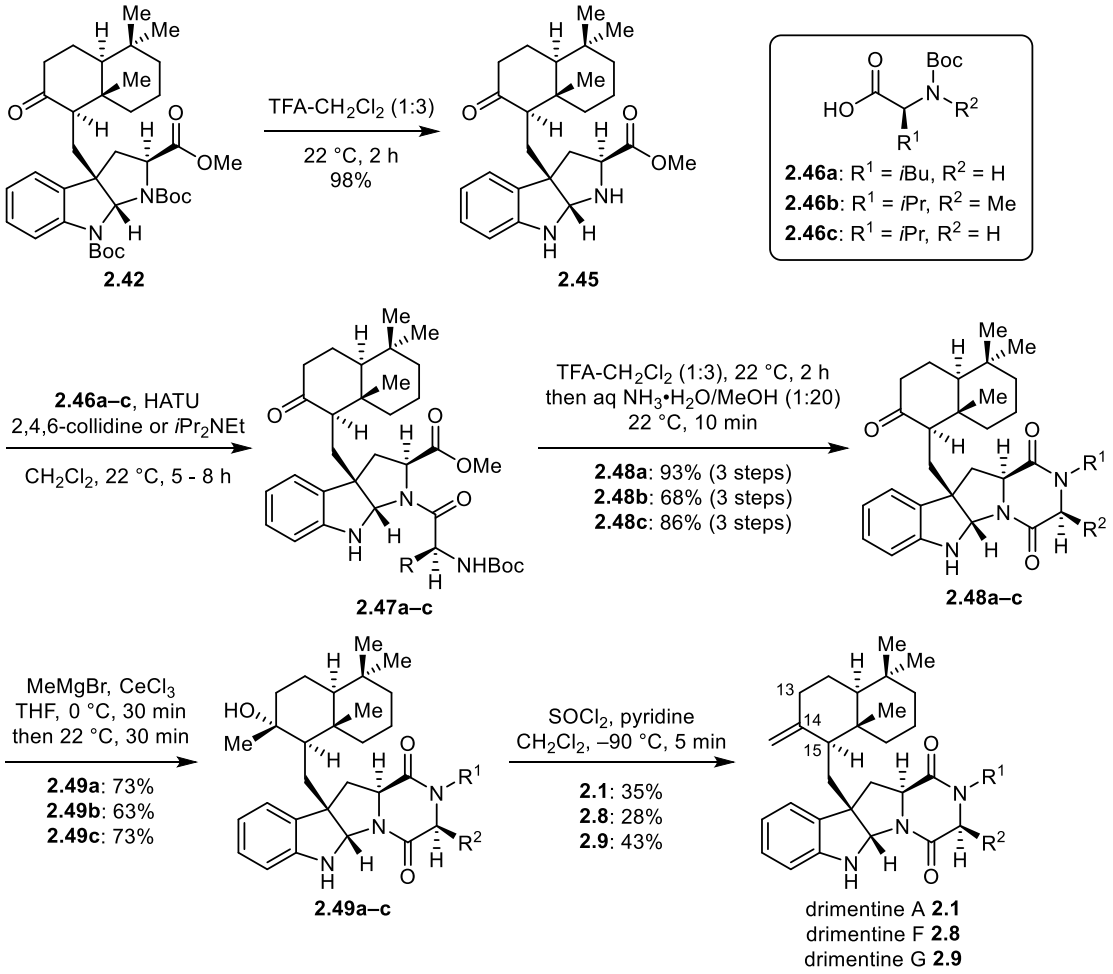
The radical conjugate addition reaction between enone **2.39** and a slight excess of bromopyrroloindoline **2.41** (1.5 equiv) was carried out in the presence of visible light photoredox catalyst [$Ir(ppy)_2(tbbpy)PF_6$] and $Et_3N$. Ketone **2.42** was produced in 91% yield[§] (Scheme 2.5); its structure was confirmed by X-ray crystallographic analysis. Other radical-based methods produced only debromination product **2.43** or homodimer **4.44**.

[§] No dr provided.



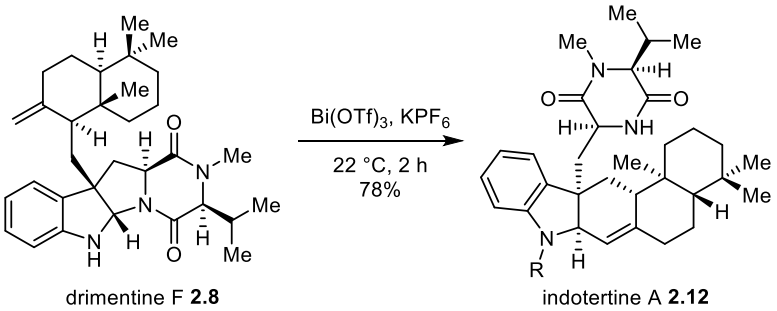

**Scheme 2.5** Radical conjugate addition of enone **2.37** and bromopyrroloindoline **2.39**

After global deprotection with trifluoroacetic acid to provide **2.45**, diketopiperazines **2.47a–c** were prepared by amide coupling with Boc-protected amino acids **2.46a–c** and base-catalyzed cyclization with aqueous ammonium hydroxide (Scheme 2.6). Numerous methylenation methods were attempted to directly convert ketones **2.48a–c** to the corresponding drimentines (**2.1**, **2.8**–**2.9**); however, all attempts failed presumably due to the steric congestion. Ketones **2.48a–c** could be converted to tertiary alcohols **2.49a–c** as single diastereomers using a methyl cerium reagent prepared *in situ* from anhydrous $CeCl_3$ and MeMgBr.[30] Attempts to dehydrate tertiary alcohols **2.49a–c** using conventional methods resulted in either no reaction or formation of the thermodynamically-favored $\Delta^{14,15}$-olefin isomer. Finally, treatment of **2.49a–c** with thionyl chloride and pyridine at –90 °C for 5 minutes[31] produced drimentines A, F, and G (**2.1**, **2.8**, and **2.9**) as mixtures with their $\Delta^{14,15}$- and $\Delta^{13,14}$-olefin isomers. Drimentine A (**2.1**) was isolated in 35% yield from a 3:4:1 mixture of isomers; drimentine F (**2.8**) was isolated in 28% yield from a 1:2.4 mixture of isomers; and drimentine G (**2.9**) was isolated in 48% yield from a 5:5:1 mixture of isomers.




**Scheme 2.6** Completion of the total synthesis of drimentines A, F, and G (**2.1**, **2.8**, and **2.9**)

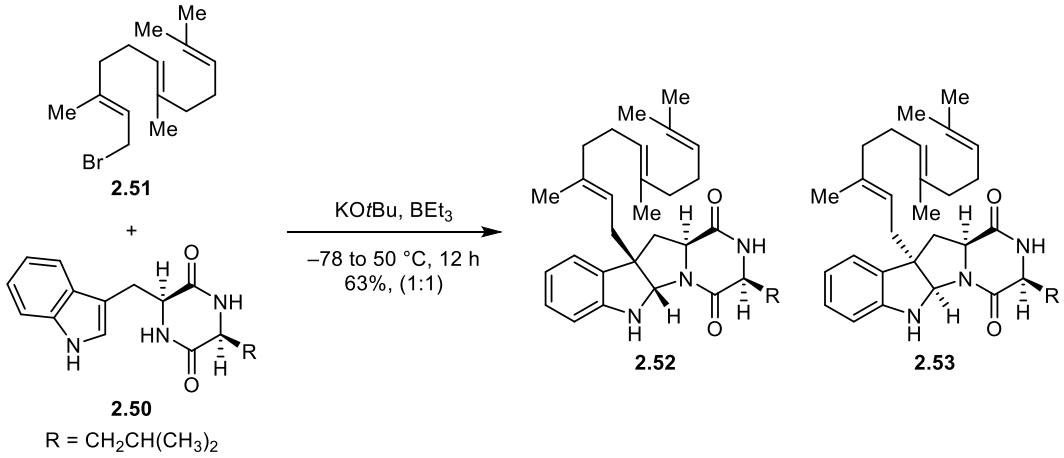
Drimentine F (**2.8**) was converted to indotertine A (**2.12**) using bismuth catalysis (Scheme 2.7). Previously bismuth had been shown to catalyze intermolecular hydroamination reactions of 1,3-dienes[32] and the direct substitution of hydroxyl groups.[33] The $Bi(OTf)_3/KPF_6$ catalyst functions both as a π-acid to activate the alkene and as a Lewis acid to control the position of the attack. Treatment of **2.8** with $Bi(OTf_3)/KPF_6$ provided **2.12** in 78% yield.




**Scheme 2.7** Conversion of drimentine F (**2.8**) into indotertine A (**2.12**)

### 2.4.2 Poupon's Biomimetic Synthesis of $\Delta^{8'}$-Isodrimentine A

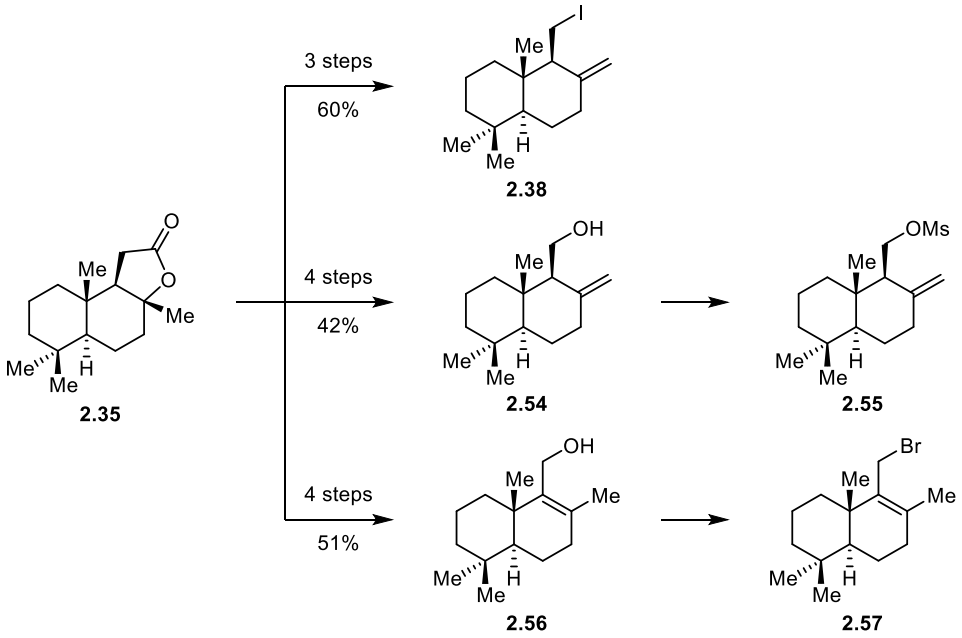
In 2016, Poupon et al.[34] were interested in conducting a biomimetic synthesis of the drimentines. Exposure of *cyclo*-L-leucine-L-proline **2.50** and farnesyl bromide **2.51** to KO*t*Bu and $BEt_3$ produced a 1:1 diastereomeric mixture of β-adduct **2.52** and α-adduct **2.53** (Scheme 2.8). These were isolated in 25% yield each.




**Scheme 2.8** Biomimetic preparation of **2.52** and **2.53**

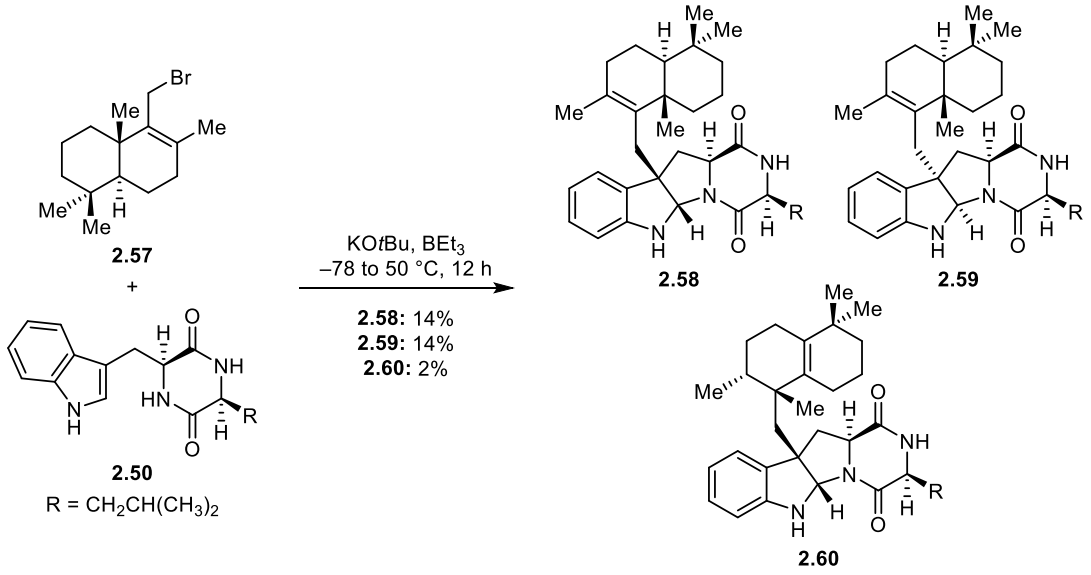
All attempts to prepare drimentine A from **2.52** via cyclization of the farnesyl group were unsuccessful, so Poupon et al. decided to attempt cyclization-alkylation using preformed drimane-type decalins (Scheme 2.9). Iodide **2.38** was prepared in 60% yield

over three steps from (+)-sclareolide (**2.35**),[28–29] and alcohol **2.54** was prepared in 42% yield over four steps from (+)-sclareolide **2.35** then mesylated to provide **2.55**.[35]




**Scheme 2.9** Preparation of drimane electrophiles **2.38**, **2.55**, and **2.57**

Unfortunately, the previously used conditions (KO*t*Bu and $BEt_3$) for the cyclization-alkylation of **2.50** were completely ineffective when homoallylic electrophiles **2.38** and **2.55** were used. So, allyl alcohol **2.56** was prepared in 51% yield over four steps from (+)-sclareolide (**2.35**) then converted to allyl bromide **2.57**.[35] When this electrophile was allowed to react with **2.50** in the presence of KO*t*Bu and $BEt_3$, a 1:1 diastereomeric mixture of $\Delta^{8'}$-isodrimentine A (**2.58**) and α-adduct **2.59** was obtained in 35% yield. When this mixture was separated by preparative HPLC, **2.58** and **2.59** were isolated in 14% yield each. Also recovered was 2% yield of **2.60**, which resulted from a Wagner–Meerwein rearrangement of **2.58**.




**Scheme 2.10** Biomimetic preparation of Δ8′-isodrimentine A (**2.58**)

## 2.5 Synthetic Proposal

Alkaloids containing a C3a-substituted hexahydropyrrolo[2,3-*b*]indole core are a large class including members with C3a-heteroatom- (**2.61**[36] and **2.62**[37]) and arene-substituents (**2.63**[38–39]) as well as homodimers (**2.64**[40]).[41] C3a-alkyl-substituted hexahydropyrrolo[2,3-*b*]indole alkaloids are also known. However, prior to isolation of the drimentines, the most complex alkyl substituents were prenyl derivatives (**2.65**[42]). The drimentines are the only pyrroloindolines with sesquiterpene substitution at the C3a-position of the hexahydropyrrolo[2,3-*b*]indole core, which makes them structurally interesting targets for total synthesis. Improvements on the reported syntheses could be made. In particular, it would be advantageous to avoid late-stage preparation of the exocyclic olefin.

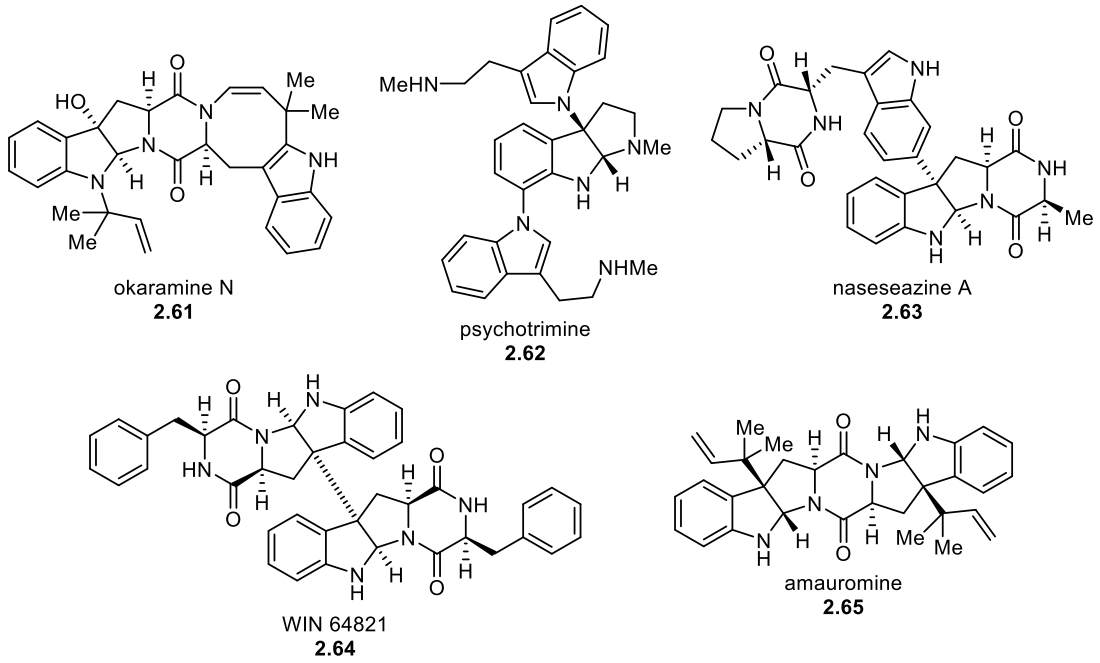



**Figure 2.4** Representative hexahydropyrrolo[2,3-*b*]indole alkaloids

While initial biological activity screenings showed only weak to moderate antibacterial, antitumor, and cytotoxic activities,[7,11,13–14] we believe that there is a high possibility of yet undiscovered reactivity and that the drimentines are a class of alkaloids that should be further studied. Additionally, the unique structure the drimentines possess may inspire novel reaction discovery. To this end, we decided to undertake a total synthesis of the drimentines beginning with drimentine C in order to provide enough material for additional assays of biological activity. In the following chapters, two synthetic routes will be discussed. The first involves retrosynthetic disconnection of the pyrroloindoline core to an oxindole, which can be prepared by asymmetric palladium-catalyzed cyanoamidation of a cyanoformamide substrate. The second involves retrosynthetic disconnection between the pyrroloindoline and sesquiterpene moieties.

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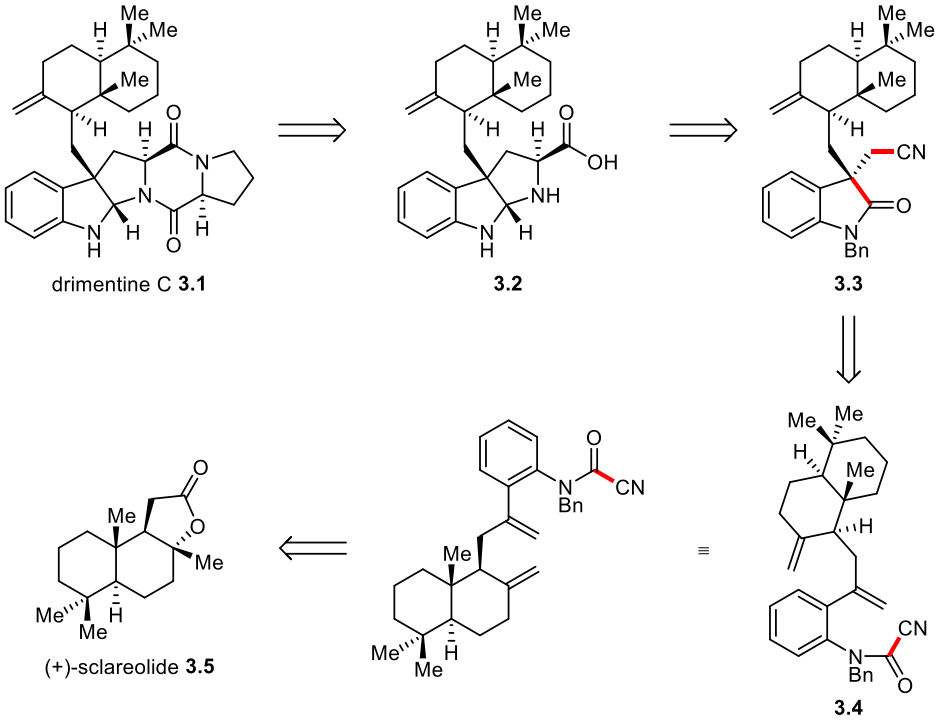
# Chapter 3: Progress Toward a Total Synthesis of Drimentine C Utilizing Palladium-Catalyzed Cyanoamidation

## 3.1 Introduction

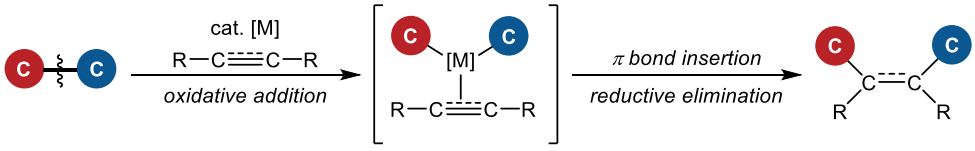
The first route to drimentine C (**3.1**) we proposed featured carbon–carbon (C–C) bond activation, namely cyanoamidation, which has been studied by our group. This route utilized late-stage formation of the diketopiperazine ring from pyrroloindoline **3.2** thereby allowing for late-stage diversification to synthesize multiple family members (Scheme 3.1). Pyrroloindoline core **3.2** would be constructed by alkylation and cyclization of oxindole **3.3**, which would result from palladium-catalyzed cyanoamidation with a chiral phosphoramidite ligand. In this reaction, the C–CN bond of cyanoformamide **3.4** is activated by low-valent palladium and added across the pendant alkene. This is an efficient and atom economical methodology for the preparation of oxindoles, which rapidly builds molecular complexity in a single step. The synthesis would begin with ring-opening and elaboration of commercially-available (+)-sclareolide (**3.5**). Overall, the synthesis of drimentine C (**3.1**) from **3.5** by this route is linear. This chapter will introduce C–CN bond activation and detail the progress made toward drimentine C (**3.1**) via this synthetic route.




**Scheme 3.1** Retrosynthetic overview of the proposed synthesis of drimentine C featuring palladium-catalyzed asymmetric cyanoamidation

## 3.2 Overview of C–CN Bond Activation

The activation of C–C σ-bonds has gained increasing attention over the past few decades. Specifically, this is the ability to selectively cleave a C–C σ-bond by oxidative addition to a transition metal with subsequent addition across a carbon–carbon multiple bond (Scheme 3.2).

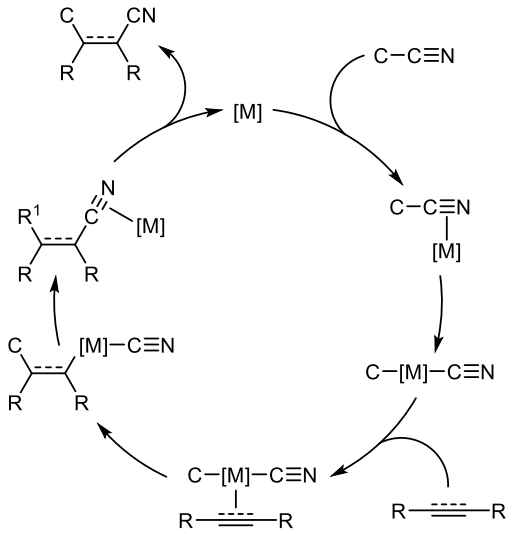



**Scheme 3.2** Catalytic C–C bond activation

In the past, C–C σ-bonds have been considered intrinsically inert from both kinetic and thermodynamic perspectives. From a kinetic perspective, C–H bonds typically outnumber and are sterically more accessible than C–C bonds. From a thermodynamic perspective, C–C bond activation must compete with C–H bond activation in terms of oxidative addition. An energetic preference for the formation of M–H bonds (60 kcal $mol^{-1}$) over M–C bonds (20-30 kcal $mol^{-1}$) makes C–C bond activation much less favorable than C–H bond activation.[1–3] Additionally, the oxidative addition of a transition metal into a C–C bond is significantly endothermic because a strong C–C bond (~90 kcal $mol^{-1}$) is sacrificed for two relatively weak M–C bonds (25 kcal $mol^{-1}$). All of these reasons contribute to placing selective C–C bond activation at a disadvantage to C–H bond activation.

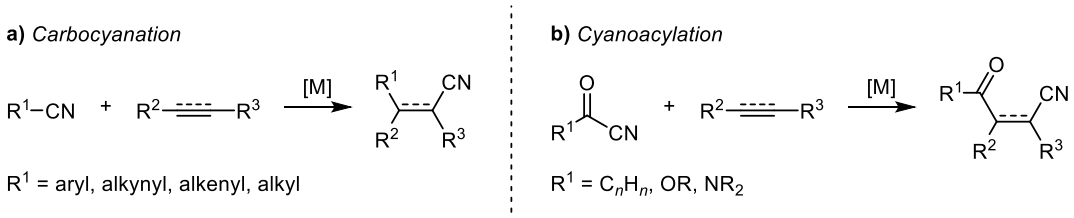
Chemists have used a variety of strategies to overcome these challenges including coupling C–C bond activation to energy-releasing steps like the relief of ring strain or aromatization. Additionally, substrates have been designed strategically incorporating a heteroatom, which coordinates to the metal and forms a metallacycle intermediate thereby directing the metal to the appropriate C–C bond.[4] However, the need for high energy starting materials or covalently-bound directing groups has limited the utility of these methodologies in organic synthesis.

Carbon–nitrile (C–CN) bond activation is able to avoid these limitations. Nitriles are important building blocks in organic synthesis; they serve as carbonyl and aminoalkyl precursors. While C–CN bonds have high dissociation energies (>100 kcal $mol^{-1}$), nitriles strongly coordinate to metals in either an $\eta^1$- or $\eta^2$-fashion making the reaction more feasible.[5] This coordination also allows the nitrile to act as a directing group for C–CN bond activation. Oxidative addition of low-valent metal complexes into aryl, alkynyl, alkenyl, alkyl, and acyl C–CN bonds has been realized; the generally accepted mechanism for C–CN bond activation is shown in Scheme 3.3. The metal coordinates to the nitrile followed by oxidative addition into the C–CN bond. The resulting C–M–CN complex coordinates to an alkene or alkyne, which undergoes carbometallation. Reductive elimination generates a product with two new C–C σ-bonds.




**Scheme 3.3** General mechanism of C–CN bond activation

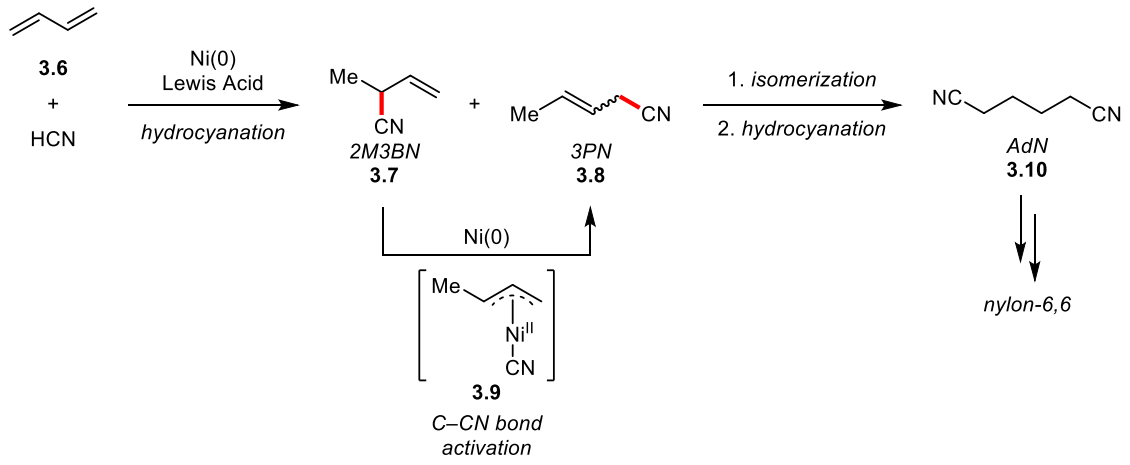
Discussed in this section are carbocyanation, a class of reactions wherein an organonitrile is added across an olefin, and its subclass cyanoacylation, where the activated bond is $C_{acyl}$–CN (Scheme 3.4). Cyanoesterification and cyanoamidation, subclasses of cyanoacylation, refer to the activation of an ester or an amide, respectively. The activation of C–CN bonds with subsequent decyanation, cross-coupling, or cycloaddition will not be discussed.[5]




**Scheme 3.4** Additions of organonitriles across alkenes/alkynes: a) carbocyanation; b) cyanoacylation

### 3.2.1 Carbocyanation

The first mention of C–CN bond activation occurred in 1971 when Burmeister and Edwards[6] reported the oxidative addition of 1,1,1-tricyanoethane to $Pd(PPh_3)_4$. The most notable early example of C–CN bond activation occurs in the DuPont synthesis of adiponitrile (AdN, **3.10**), a precursor to nylon-6,6 (Scheme 3.5).[7–10] Hydrocyanation of 1,3-butadiene (**3.6**) using a combination of Ni(0) and Lewis acid catalysis produces a 1:1.5 mixture of regioisomers: 2-methyl-3-butenenitrile (2M3BN, **3.7**) and 3-pentenenitrile (3PN, **3.8**). Isomerization of undesired **3.7** to **3.8** is carried out using Lewis acid-assisted C–CN bond activation via Ni(II) π-allyl cyanide intermediate **3.9**.[11] 3PN (**3.8**) subsequently undergoes additional isomerization and hydrocyanation reactions to generate AdN (**3.10**). Detailed mechanistic studies of this process have been carried out determining the critical role of Lewis acid in the hydrocyanation and carbocyanation steps, which has served as an inspiration for carbocyanation methodology development.[12]



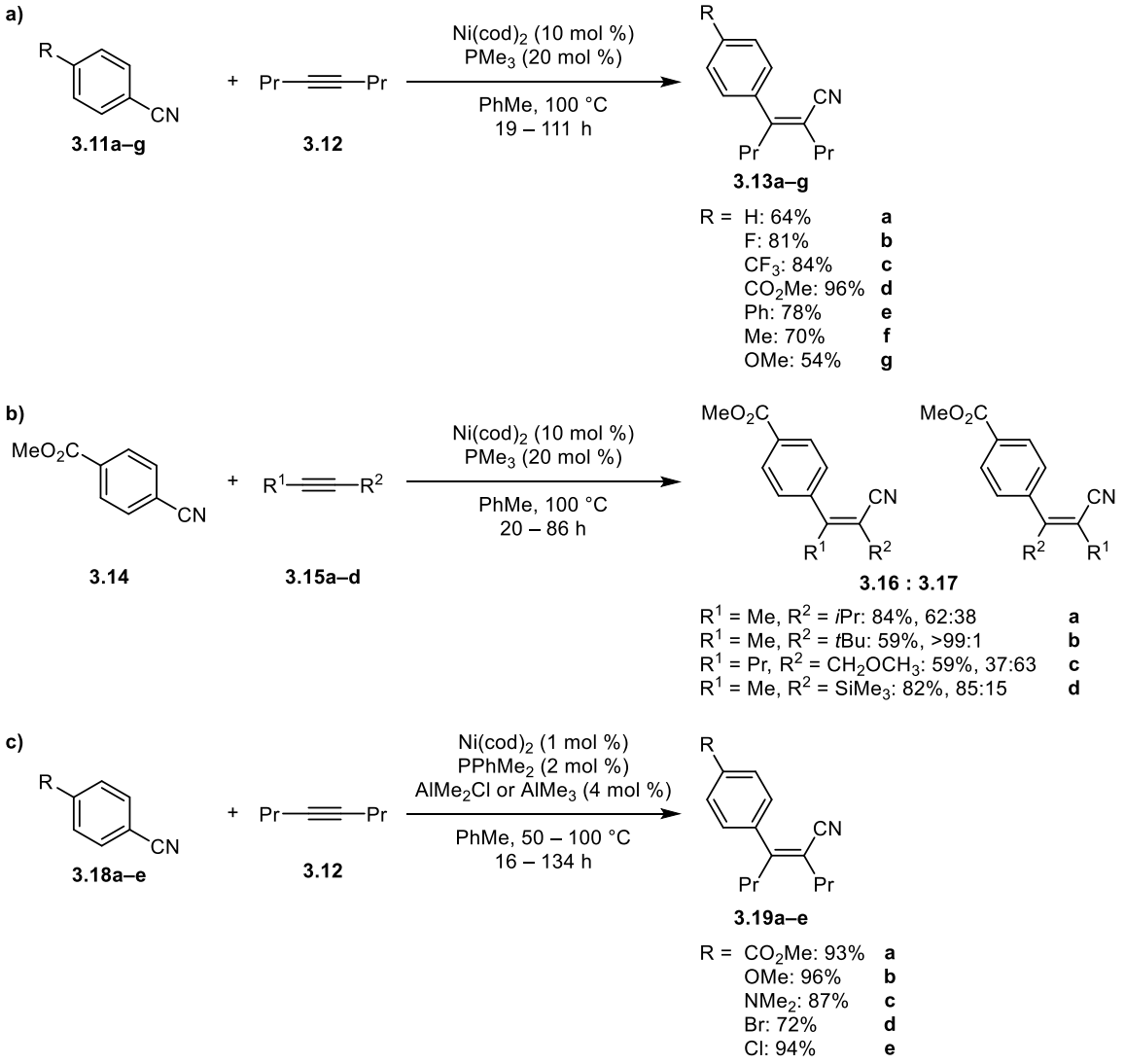

**Scheme 3.5** Nickel-catalyzed C–CN bond activation in DuPont's adiponitrile synthesis

In 2004, Nakao and Hiyama and coworkers[13–14] reported the first arylcyanation reaction. Using $Ni(cod)_2$ with $PMe_3$ (1:2) as the catalyst system, the C–CN bond of benzonitrile **3.11** was activated and added across 4-octyne **3.12** providing (*Z*)-3-phenyl-2-propyl-3-hexenenitrile **3.13a** in 64% yield (Scheme 3.6a). Benzonitriles with electron-

withdrawing substituents at the 4-position of the aryl ring were more reactive, providing the β-arylalkene nitrile products (**3.13b–d**, 19–30 hours) in good to excellent yields. The presence of electron donating substituents *para*- to the nitrile reduced the reaction rate, resulting in lower yields (**3.13e–g**, 40–111 hours). From these observations, the authors hypothesized that oxidative addition of the C–CN bond to the Ni(0) catalyst was likely the rate determining step.

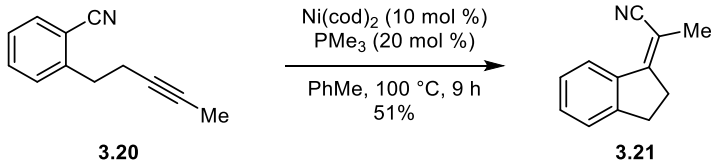
When unsymmetrical alkynes (**3.15a–d**) were employed in the reaction with benzonitrile **3.14**, mixtures of regioisomers **3.16** and **3.17** were prepared (Scheme 3.6b). The predominant regioisomer was **3.16** where the aryl group was attached to the less-hindered alkyne carbon. A subsequent DFT study suggested that the alkyne first inserts into the Ni–Ar bond (arylnickelation) and that the regioselectivity arises from minimization of steric repulsion between the aryl group and the larger $R^2$ group.[15]

A dramatic effect was seen when Lewis acids, which are known to improve oxidation of C–CN bonds by coordinating to the lone pair of the nitrile,[12] were employed in the arylcyanation reaction.[16] Addition of $AlMe_2Cl$ or $AlMe_3$ (4 mol %) allowed for a reduction in catalyst loading and a lowering of reaction temperature (Scheme 3.6c). Additionally, benzonitriles with electron-donating substituents *para*- to the nitrile now underwent the reaction in good yields (**3.19b**: R = OMe, 96%, 16 hours, 50 °C; **3.19c**: R = $NMe_2$, 87%, 21 hours, 50 °C). Reactivity in the presence of electron-withdrawing substituents was maintained **(3.19a–b**). Of note, under these conditions, the Ar–CN bond was selectively cleaved in the presence of Ar–halogen bonds (**3.19d**: R = Br, 72%, 27 hours, 50 °C; **3.19e**: R = Cl, 94%, 18 hours, 50 °C). Regioselectivity when using unsymmetrical alkynes remained unchanged.




**Scheme 3.6** Nickel-catalyzed intermolecular arylcyanation of alkynes: a) scope of benzonitrile; b) using unsymmetrical alkynes; c) with Lewis acid co-catalysis

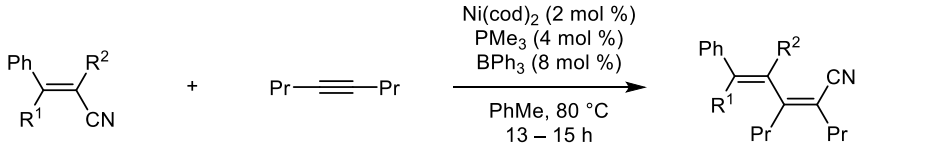
In addition to the intermolecular reactions discussed thus far, carbocyanation of alkynes with aryl cyanides was also extended to an intramolecular variant (Scheme 3.7).[14] Benzonitrile **3.20** underwent a 5-*exo*-dig cyclization upon treatment with $Ni(cod)_2$ and $PMe_3$. Indene product **3.21**, featuring an exocyclic olefin, was obtained in 51% yield; the structure was confirmed by X-ray crystallographic analysis.




**3.20** **3.21**

**Scheme 3.7** Intramolecular carbocyanation of aryl nitriles with alkynes

The use of Lewis acid additives allowed the scope of nickel-catalyzed carbocyanation to be extended to alkenyl cyanides.[16] Di- and trisubstituted vinyl nitriles (**3.22a–b**, Scheme 3.8) underwent carbocyanation with 4-octyne **3.12** using $Ni(cod)_2$ (2 mol %) with $PMe_3$ (4 mol %) and $BPh_3$ (8 mol %) to provide 1,3-dienes (**3.23a–b**) in excellent yields (81–95%) without oligomerization. Additionally, carbocyanation of benzylidenemalonitrile **3.22c** occurred regioselectively with C–CN bond activation occurring preferentially at the cyano group *trans*- to the phenyl ring.




**3.22a–c** 1:1.2 **3.12** **3.23a–c**

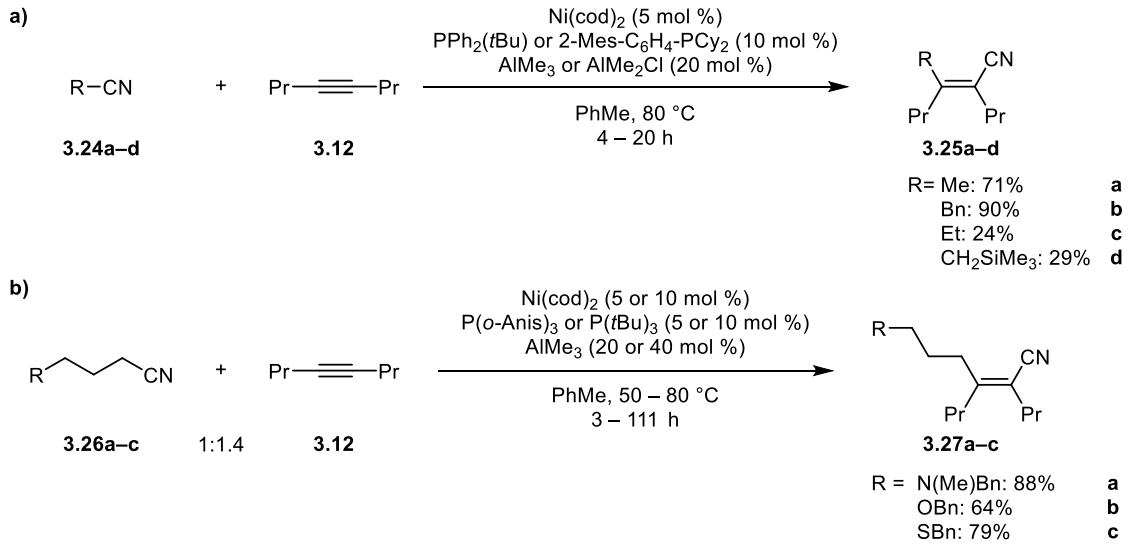
$R^1$, $R^2$ = H: 95% **a**
$R^1$ = Ph, $R^2$ = H: 94% **b**
$R^1$ = H, $R^2$ = CN: 81% **c**

**Scheme 3.8** Nickel/Lewis acid-catalyzed intermolecular alkenylcyanation of alkynes

The extension of carbocyanation to alkyl nitriles met with preliminary success. Treatment of acetonitrile **3.24a** and 4-octyne **3.12** with $Ni(cod)_2$ (5 mol %), $PPh_2(tBu)$ (10 mol %), and $AlMe_3$ (20 mol %) provided alkylcyanation product **3.25a** in 71% yield (Scheme 3.9a).[16] Changing the catalyst system to $Ni(cod)_2$ (2 mol %), 2-Mes-$C_6H_4$-$PCy_2$ (4 mol %), and $AlMe_2Cl$ (8 mol %) allowed for alkylcyanation of benzylnitrile **3.24b** accessing **3.25b** in 90% yield.[17] However, alkylcyanation of substrates containing β-hydrogens, including propionitrile **3.24c** and (trimethylsilyl)acetonitrile **3.24d**, provided products in less than 30% yield. Instead, hydrocyanation was observed resulting from a

competing β-hydride elimination pathway.

Hydrocyanation could be minimized when the alkyl cyanide substrates were designed with a heteroatom (O, N, S) at the γ-position (Scheme 3.9b). Nakao and Hiyama et al.[18] proposed that the heteroatom coordinates to the metal center forming a five-membered metallacycle. In this proposed intermediate, the β-hydrogens are no longer *syn*-coplanar to the metal. Additionally, once the γ-heteroatom and the cyano group have coordinated, the metal no longer has available vacant coordination sites. Both of these features would work to slow β-hydride elimination. Alkyl cyanides **3.26a–c** underwent cyanoamidation with 4-octyne **3.12** to provide alkenes **3.27a–c** in good yields (64–88%).

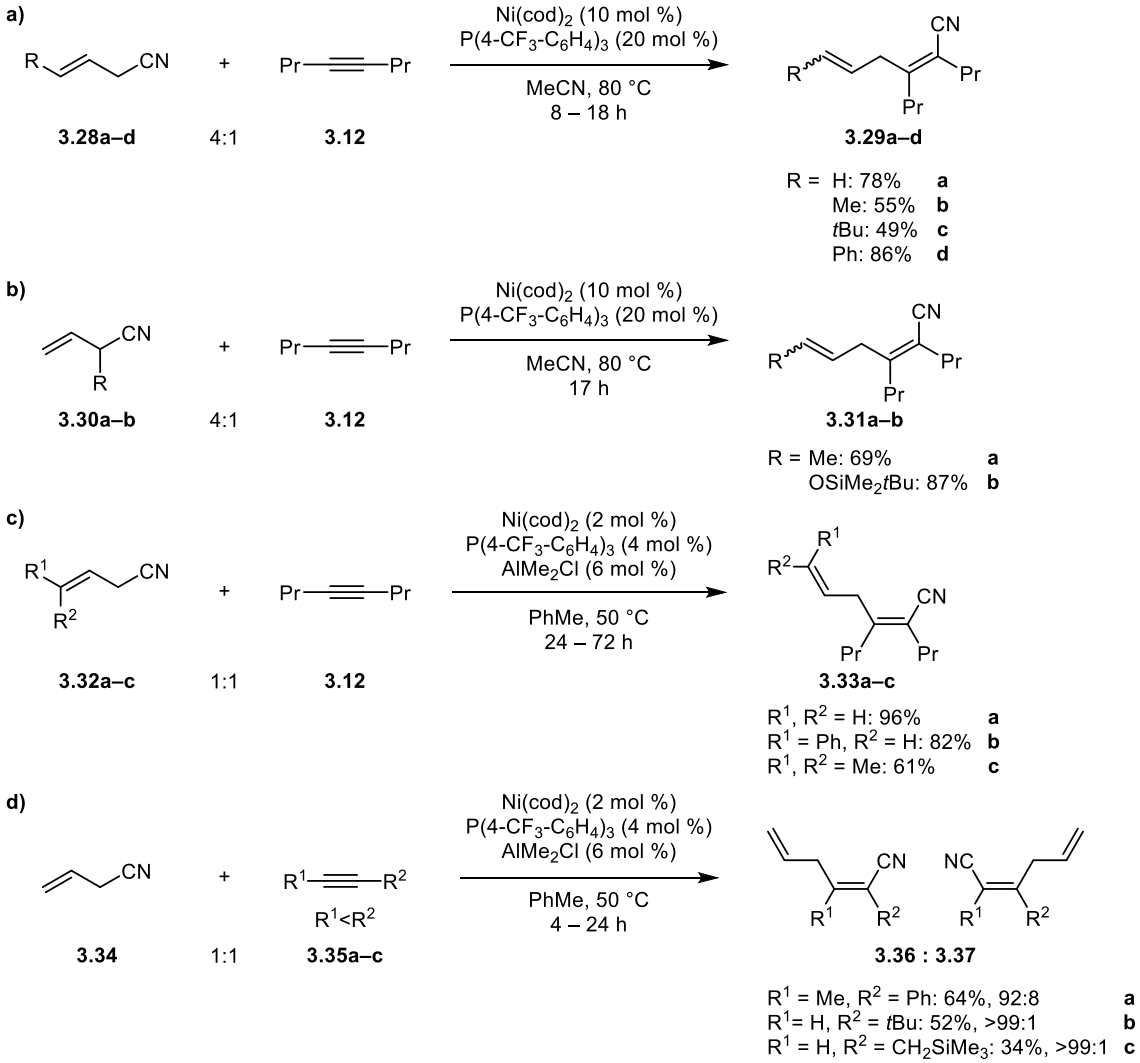



**Scheme 3.9** Nickel/Lewis acid-catalyzed intermolecular carbocyanation of alkynes: a) alkylcyanation; b) heteroatom-directed alkylcyanation

Inspired by the DuPont adiponitrile synthesis, Nakao and Hiyama et al.[19] further developed the allylcyanation of alkynes. Surprisingly, allylic nitriles did not undergo carbocyanation under the optimal conditions for aryl- and alkenylcyanation. Instead, an electron-deficient phosphine, P(4-$CF_3$-$C_6H_4$)$_3$, was required for reactivity. Acetonitrile was found to be a better solvent than toluene. A competitive C–H bond activation pathway was operational, so excess allylic nitrile (4.0 equiv) was required to overcome

substrate loss due to olefin isomerization. However, using these conditions, allylic cyanides **3.28a–d** underwent allylcyanation with 4-octyne **3.12** to produce 1,4-dienes **3.29a–d** in moderate yields (49–85%, Scheme 3.10a). The substrate scope for this reaction was narrow: the reaction did not tolerate γ,γ-disubstituted alkenes (Scheme 3.10b), and terminal alkynes underwent rapid oligomerization.

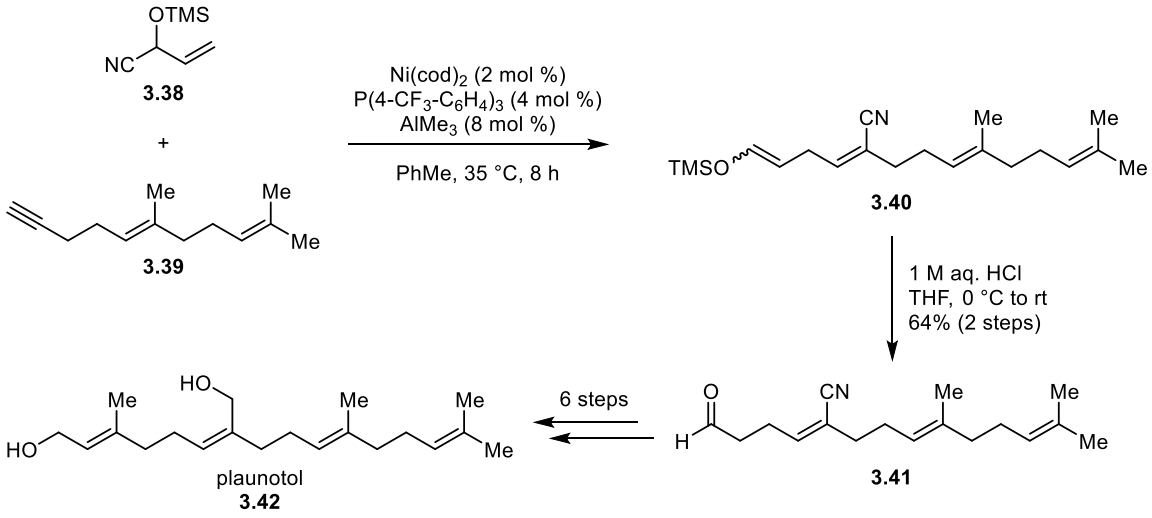
Addition of Lewis acid ($AlMe_2Cl$, 6 mol %) greatly improved the nickel-catalyzed allylcyanation reaction.[20] C–H bond activation was effectively minimized, allowing for an equimolar reaction between **3.32** and **3.12** (Scheme 3.10c). Additionally, both catalyst loading and reaction temperature could be decreased, which suppressed oligomerization thereby extending the scope of the reaction to terminal olefins (Scheme 3.10d). Allylcyanation of unsymmetrical alkynes **3.35a–c** with allyl cyanide **3.34** proceeded in good yields (34–65%) and excellent regioselectivities, favoring product **3.36** with the larger group of the alkyne ($R^2$) on the same side as the nitrile.




**Scheme 3.10** Nickel-catalyzed intermolecular carbocyanation of alkynes with allyl nitriles: a) scope without Lewis acid; b) scope with γ-heteroatom; c) scope with Lewis acid; d) regioselectivity using unsymmetrical alkynes

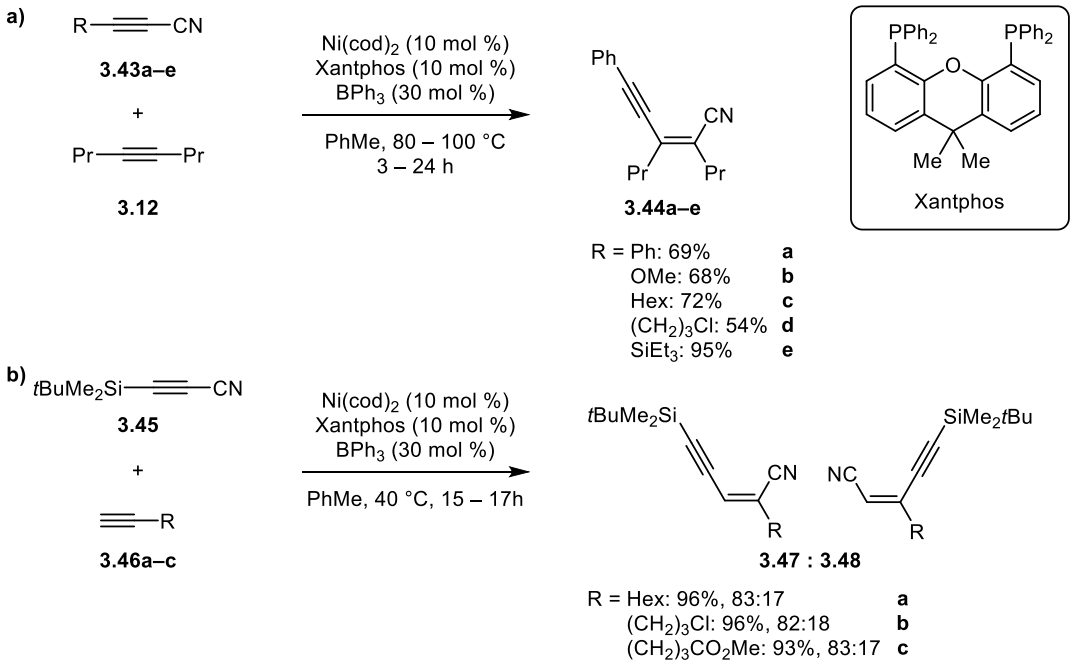
The intermolecular nickel/Lewis acid-catalyzed allylcyanation reaction was highlighted in the total synthesis of plaunotol, an antibacterial natural product active against *Helicobacter pylon* (Scheme 3.11).[20] The reaction of α-silyloxyallyl cyanide **3.38** and terminal alkyne **3.39** provided silyl enol ether **3.40** on gram scale with 94:4 regioselectivity. Subsequent acidic hydrolysis of **3.40** provided aldehyde **3.41** in 64%

yield over the two steps.




**Scheme 3.11** Synthesis of plaunotol (**3.42**) via nickel/Lewis acid-catalyzed intermolecular allylcyanation

Further extending the utility of carbocyanation, Nakao and Hiyama and coworkers[21–22] reported the first example of alkynylcyanation in 2008. In the presence of $Ni(cod)_2$ (10 mol %), Xantphos (10 mol %), and $BPh_3$ (30 mol %), alkynyl cyanide **3.43a** was activated and added across 4-octyne **3.12** resulting in conjugated enyne **3.44a** in 69% yield (Scheme 3.12a). The bidentate ligand, Xantphos, was required for reactivity; monodentate phosphines provided only minimally detectable amounts of product. The Lewis acid co-catalyst minimized competing homocyclotrimerization and promoted the desired C–CN bond activation. Internal alkynyl cyanides underwent alkynylcyanation with **3.12** providing the corresponding enyne products **3.44** in good to excellent yields (**3.44b–e**, 54–95%).

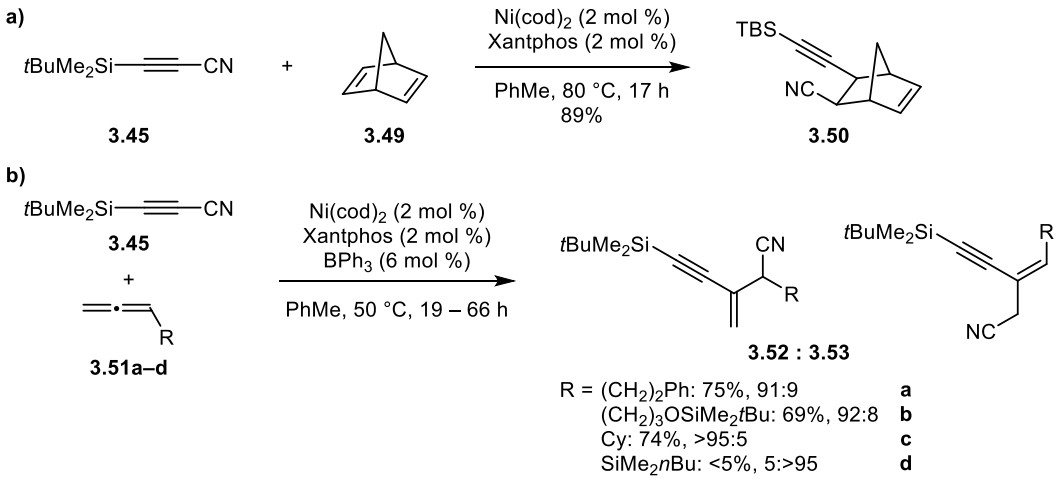



**Scheme 3.12** Nickel/Lewis acid-catalyzed intermolecular alkynylcyanation of alkynes: a) alkynyl cyanide scope; b) alkyne scope and regioselectivity

Terminal alkynes were also viable substrates, undergoing alkynylcyanation with alkynyl cyanide **3.45** in excellent yields and regioselectivities (**3.47:3.48a–c**, 93–96%). Regioisomer **3.47** with the alkynyl group attached to the less-substituted carbon was favored. This would result from the alkynyl group of alkynyl cyanide **3.45** undergoing migratory insertion into the less hindered carbon of the coordinating alkyne (**3.46**).

Thus far, all examples discussed have featured C–CN bond activation and addition to alkynes. The carbocyanation of alkenes is inherently more challenging due to the reluctance of alkenes to undergo migratory insertion relative to alkynes.[23] Additionally, β-hydride elimination, which would produce Heck-like products, is preferred over reductive elimination. In 2009, Nakao and Hiyama et al.[22] reported an attempt to add alkynyl cyanides across alkenes. Unfortunately, all reactions using simple alkene substrates (1-octane, styrene, and 1,3-dodecadiene) were unsuccessful under a variety of conditions. However, when strained bicyclic alkenes were used, carbocyanation occurred. Reaction of alkynyl cyanide **3.45** with norbornadiene **3.49**

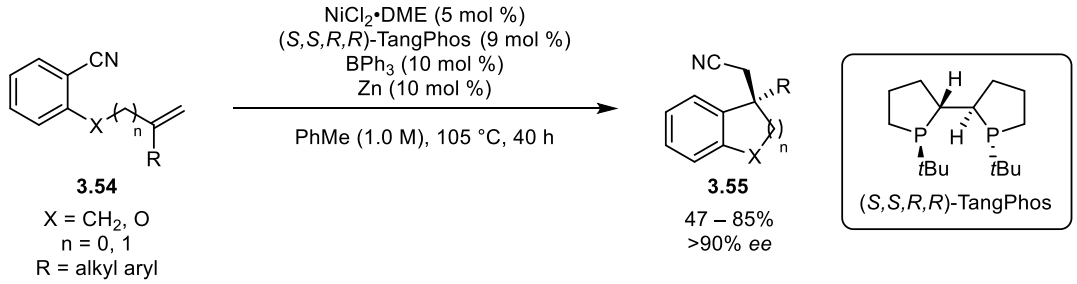
using $Ni(cod)_2$ (2 mol %) and Xantphos (2 mol %) in toluene at 80 °C afforded *exo-cis*-alkynylation product **3.50** in 89% yield (Scheme 3.13a). Lewis acids did not improve reactivity. The success of this substrate was attributed to minimization of the β-hydride elimination pathway. In conformationally-restricted norbornadiene, there are no accessible *syn*-β-hydrogens. The alkynylation of 1,2-dienes was feasible under similar conditions (Scheme 3.13b).[22] Alkynyl cyanide **3.45** added across **3.51** producing a mixture of conjugated enyne regioisomers, **3.52** and **3.53**. Enyne **3.52** was formed preferentially. Mechanistically, this would result from **3.45** oxidatively adding to the nickel followed by coordination of **3.51** at the terminal double bond. Transfer of the alkynyl group to the central carbon of **3.51** would provide a π-allyl nickel species. Steric interaction between the bulky bidentate ligand and the R group would lead to preferential delivery of the nitrile vicinal to the R group.




**Scheme 3.13** Nickel-catalyzed intermolecular alkynylcyanation of alkenes: a) norbornene; b) 1,2-dienes

In 2008, the first examples of asymmetric intramolecular carbocyanation were reported. Using $Ni(cod)_2$ (5 mol %) and $PMe_3$ (10 mol %) with added Lewis acid ($BPh_3$, 10 mol %), Watson and Jacobsen[24] demonstrated the carbocyanation of aryl cyanide **3.54** producing indane **3.55** (Scheme 3.14). Of the mono- and bidentate chiral phosphines

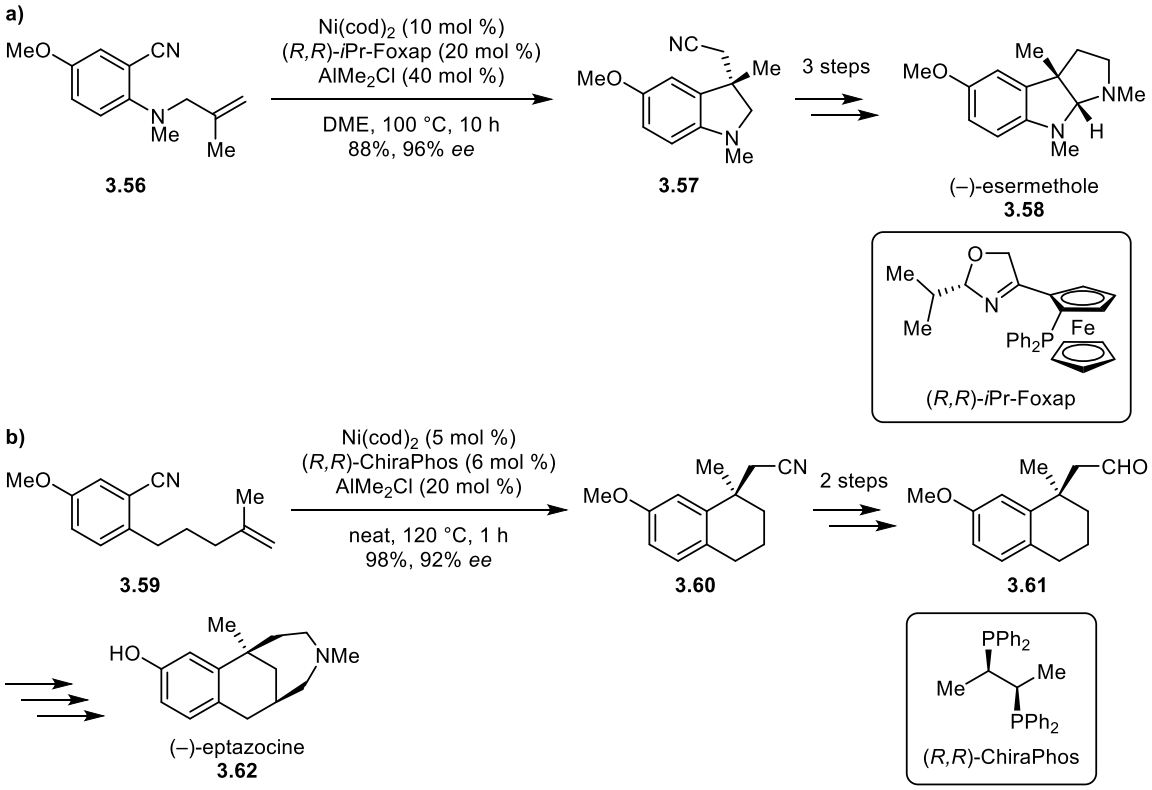
surveyed, (*S,S,R,R*)-TangPhos provided **3.55** with the highest enantioselectivity (90% *ee*). However, **3.55** was obtained in low yield (8%) due to competing olefin isomerization. *In situ* reduction of $NiCl_2$•DME with $Zn^0$ (10 mol %) suppressed the undesired isomerization. The identity of the Lewis acid affected the enantioselectivity of the reaction; $BPh_3$ proved optimal. Likely, the Lewis acid remains bound to the nitrile throughout the enantiodetermining step, which would account for this observation. Overall, dihydroindanes (**3.55**: X = $CH_2$, n = 0) and dihydrobenzopyrans (**3.55**: X = O, n = 1) could be prepared in good to excellent yields (47–85%) and enantioselectivities (>90% *ee*). However, substrates with an allylic ether tether did not undergo the reaction. Complete catalyst inhibition was observed, likely due to the competitive formation of an inactive π-allyl–nickel complex.




**Scheme 3.14** Enantioselective intramolecular arylcyanation of alkenes

Nakao and Hiyama et al.[25] utilized asymmetric intramolecular arylcyanation in the total syntheses of two natural products, (–)-esermethole and (–)-eptazocine. Using conditions similar to those of Johnson ($Ni(cod)_2$ (10 mol %), chiral phosphine ligand ((*R,R*)-*i*Pr-Foxap, 20 mol %), and $AlMe_2Cl$ (40 mol %)), dihydroindole **3.57** was prepared from **3.56** in 89% yield and 96% *ee* (Scheme 3.15a). Further elaboration completed the total synthesis of (–)-esermethole (**3.58**). Many other amino-tethered substrates were shown to undergo arylcyanation using similar conditions.[26] Likewise, tetrahydronaphthalene **3.60** was prepared from **3.59** in 98% yield and 92% *ee* using $Ni(cod)_2$ (5 mol %), (*R,R*)-ChiraPhos (6 mol %), and $AlMe_2Cl$ (20 mol %). It was

converted to synthetic precursor **3.61** in two steps, completing the formal synthesis of (–)-eptazocine (**3.62**).

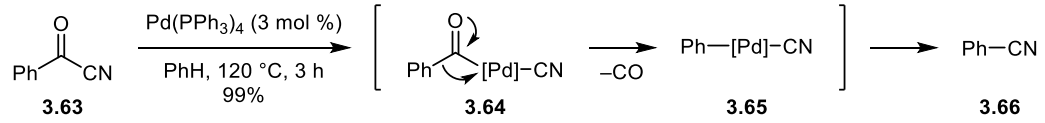



**Scheme 3.15** Enantioselective intramolecular arylcyanation of alkenes in total synthesis: a) (–)-esermethole; b) (–)-eptazocine

### 3.2.2 Cyanoacylation

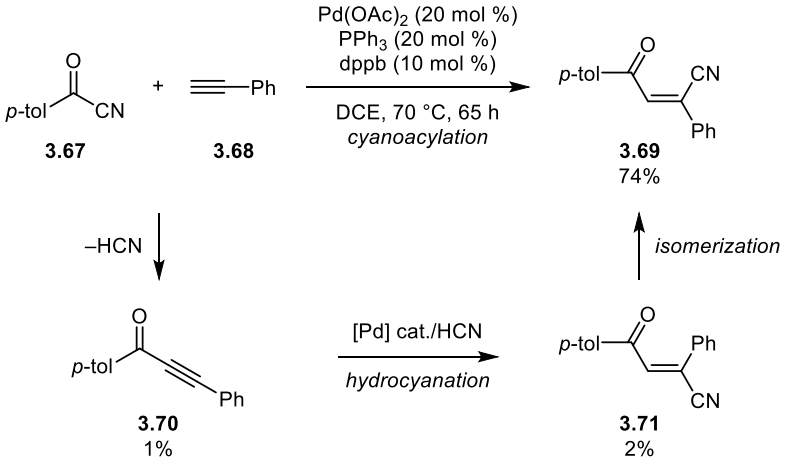
Cyanoacylation, a subset of carbocyanation reactions which involve $C_{acyl}$–CN bond activation, is substantially more facile than the previously discussed carbocyanation reactions. $C_{acyl}$–C bonds are more polarized; therefore, they undergo oxidative addition to transition metals more readily. In an initial report of $C_{acyl}$–CN bond activation, Blum et al.[27] noted that at high temperature (300 °C), aryl acyl nitriles underwent rhodium-catalyzed decarbonylation. This was extended to palladium-catalyzed decarbonylation by Murahashi et al.[28] in 1986. At 120 °C, benzoyl cyanide **3.63** oxidatively added to

$Pd(PPh_3)_4$ to give palladium complex **3.64** (Scheme 3.16). Loss of CO provided intermediate **3.65**, which underwent reductive elimination to generate benzonitrile **3.66** in 99% yield.



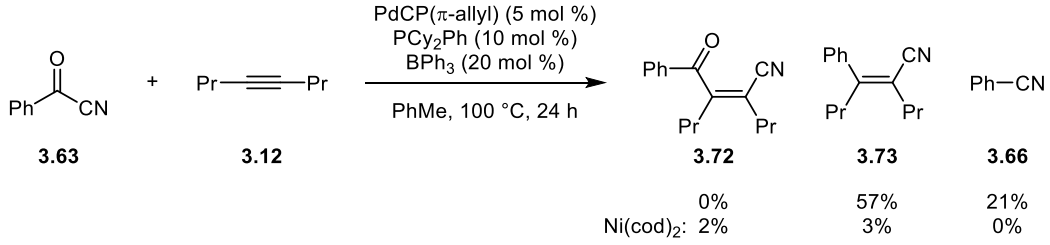

**Scheme 3.16** Palladium-catalyzed decarbonylation of acyl nitriles

In 1994, Takaya[29] reported that under palladium-catalysis, aryl acyl nitriles added across alkynes to provide cyanoacylation products. When **3.67** was reacted with terminal alkyne **3.68** in the presence of $Pd(OAc)_2$ (20 mol %) with added $PPh_3$ (20 mol %) and dppb (10 mol %), (*Z*)-alkene **3.69** was obtained in 74% yield with trace amounts of regioisomer **3.71** (2%) and acetylenic ketone **3.70** (1%) (Scheme 3.17). The authors noted that the ratio of products varied greatly, depending on the identities of the catalyst, ligands, and solvent. While **3.69** could have resulted from direct cyanoacylation, it may have been formed via an alternative pathway. Oxidative addition of **3.67** followed by loss of HCN would result in acetylenic ketone **3.70**. Hydrocyanation of **3.70** would produce **3.71**, which could undergo isomerization to ultimately produce **3.69** as the observed product.




**Scheme 3.17** Presumed acylcyanation of terminal alkynes

Nakao and Hiyama et al.[30] attempted an acylcyanation reaction of 4-octyne **3.12** with aryl acyl nitrile **3.63** using PdCp(π-allyl) (5 mol %) and $PCy_2Ph$ (10 mol %) with added $BPh_3$ (20 mol %). However, acylcyanation product **3.72** was not observed (Scheme 3.18). Instead, they isolated decarbonylation products, aryl alkene **3.73** and benzonitrile **3.66**, in 57% and 27% yield, respectively. However, changing the catalyst to $Ni(cod)_2$ provided cyanoacylation product **3.72** in 2% yield with no observed benzonitrile **3.66**.

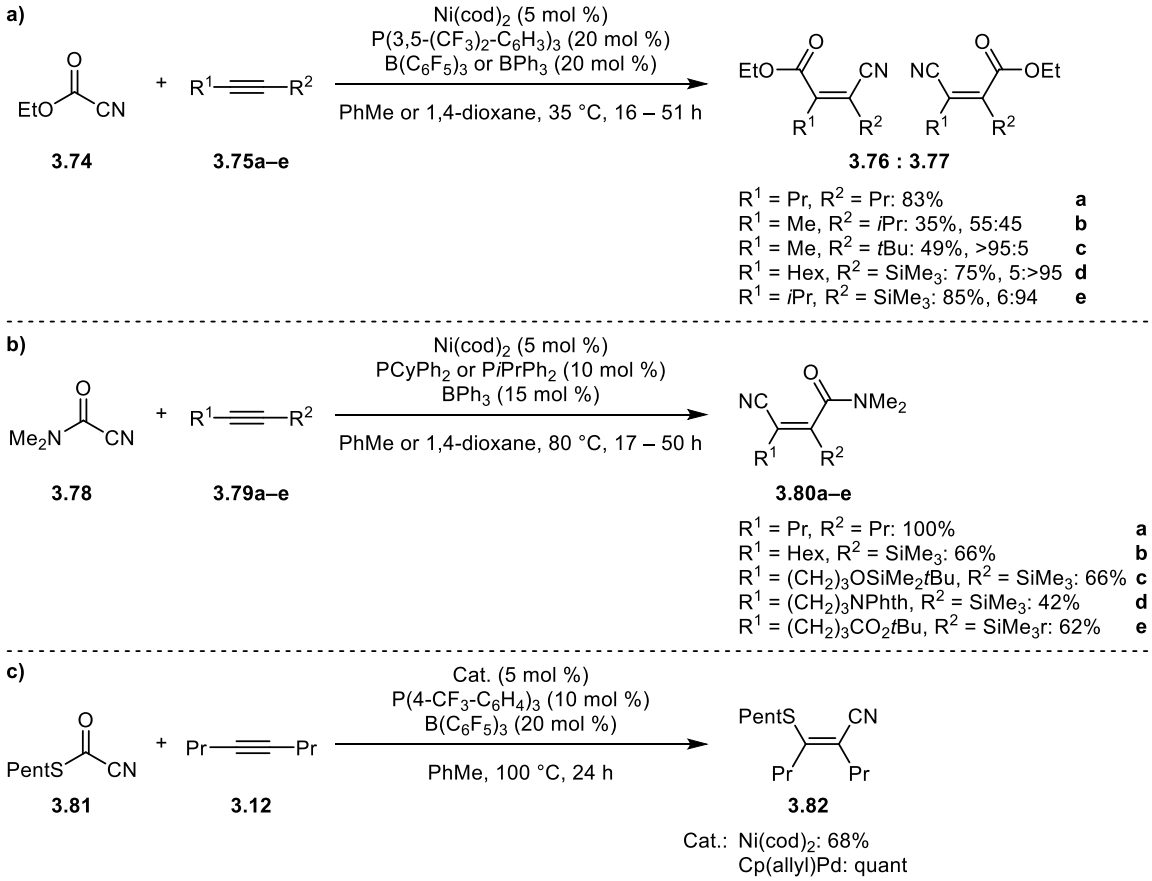



**Scheme 3.18** Attempted intermolecular acylcyanation of alkynes

Cyanoformates and cyanoformamides have proven to be more promising substrates in cyanoacylation reactions than ketonitriles. Electron-donation from the heteroatom stabilizes the carbonyl in these substrates, making them less prone to decarbonylation. Nakao and Hiyama et al.[30] demonstrated cyanoesterification in 2010 by

adding ethyl cyanoformate **3.74** across 4-octyne **3.75a** using nickel catalysis to give enoate **3.76a** in 80% yield (Scheme 3.19a). Choice of ligand and Lewis acid were key in promoting reactivity. The ligands optimal for arylcyanation of alkynes ($PMe_3$ and $PMe_2Ph$) were completely ineffective as were electron-neutral ($PPh_3$) or electron-donating ($P(4\text{-}OMe\text{-}C_6H_4)_3$) ligands. Ultimately, electron-deficient ligands ($P(4\text{-}CF_3\text{-}C_6H_4)_3$ and $P(3,5\text{-}(CF_3)_2\text{-}C_6H_3)_3$) proved optimal. Reaction with organoaluminum Lewis acids or no Lewis acid did not provide product. Triphenylborane showed limited reactivity at 100 °C (35% yield). However, addition of the more Lewis acidic $B(C_6F_5)_3$ promoted cyanoesterification, allowing the reaction to be conducted at 35 °C with good yield (74%). When using unsymmetrical alkynes, delivery of the nitrile to the most hindered carbon was favored. This was rationalized as minimization of the steric repulsion between the larger alkyne substituent ($R^2$) and the ester.

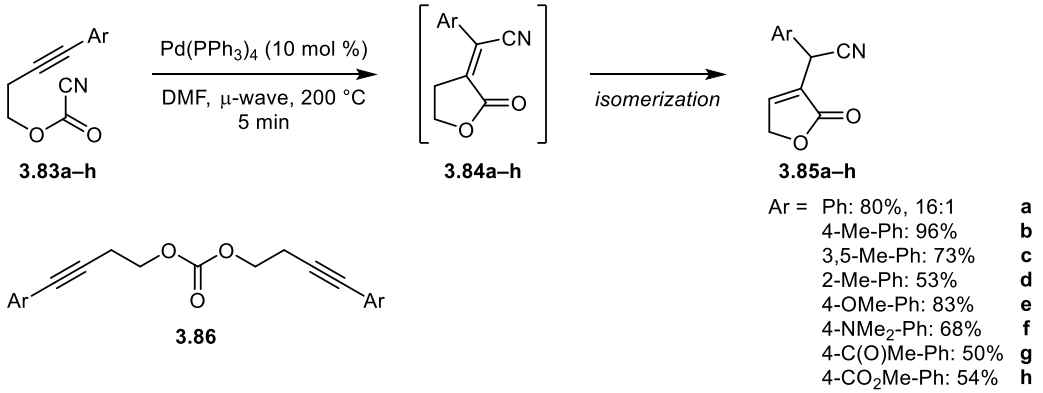
The optimal conditions for cyanoesterification were not effective when the cyanoformate was exchanged for a cyanoformamide (Scheme 3.19b).[30] Instead, reaction of cyanoformamide **3.78** with alkynes **3.79a–e** was promoted with $Ni(cod)_2$ (5 mol %), electron-donating bulky ligands ($PCyPh_2$ or P*i*$PrPh_2$, 10 mol %), and the less Lewis acidic $BPh_3$ (15 mol %). Good to excellent yields of the β-cyano-substituted acrylamides **3.80a–e** were produced. Interestingly, reactions with unsymmetrical alkynes resulted in delivery of the nitrile to the least hindered carbon of the alkyne. Likely, the Lewis acid binds to the basic carbonyl oxygen of the cyanoformamide making the resulting adduct less nucleophilic and more reluctant to undergo migratory insertion. Therefore, the nitrile would be the first group added to the alkyne at the more sterically accessible carbon, leading to the observed regioselectivity. Unlike the cyanoformate and cyanoformamide substrates, analogous cyanothiate **3.81** underwent decarbonylation prior to alkyne insertion (Scheme 3.19c). Alkene **3.82** was produced under both palladium- and nickel-catalysis.




**Scheme 3.19** Nickel/Lewis acid-catalyzed intermolecular acylcyanation of alkynes: a) cyanoesterification; b) cyanoamidation; c) decarbonylative thiocyanation

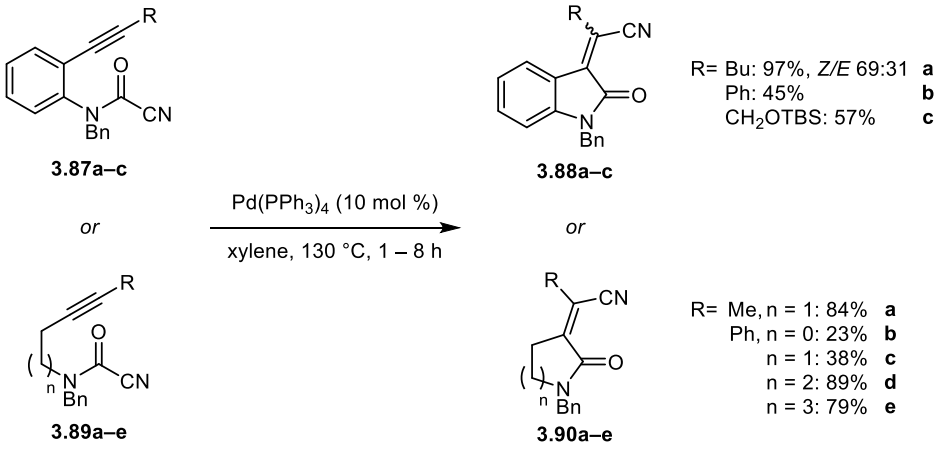
In 2011, our group[31] reported an intramolecular cyanoesterification reaction of alkynes. Reaction of cyanoformate **3.83a** with $Pd(PPh_3)_4$ in toluene at 115 °C for 48 hours resulted in 17% yield of a mixture of butenolide **3.85a** and carbonate **3.86** (Scheme 3.20). Cyanoesterification product **3.84a** had isomerized upon workup to endocyclic **3.85a**. Carbonate **3.86** was proposed to result from decarbonylation of the oxidative addition adduct followed by disproportionation. Use of a Lewis basic solvent, DMF, improved selectivity for **3.85a**. Lewis acidic conditions were not explored. Additionally, increasing the reaction temperature with shortened reaction times improved the yield of **3.85a**. Ultimately treatment of **3.83a** with $Pd(PPh_3)_4$ (10 mol %) in DMF at 200 °C for 5 minutes in a microwave reactor provided **3.85a** in 80% yield. In regard to substitution on

the aromatic ring, substituents at the *ortho*-, *meta*-, and *para*-positions were all tolerated (**3.85b–d**). Electron-donating substituents provided the corresponding butenolides in good yields (**3.85e**: 83%, **3.85f**: 68%), while electron-withdrawing substituents provided the corresponding butenolides in slightly diminished yields (**3.85g**: 50%, **3.85h**: 54%).




**Scheme 3.20** Palladium-catalyzed intramolecular cyanoesterification of alkynes

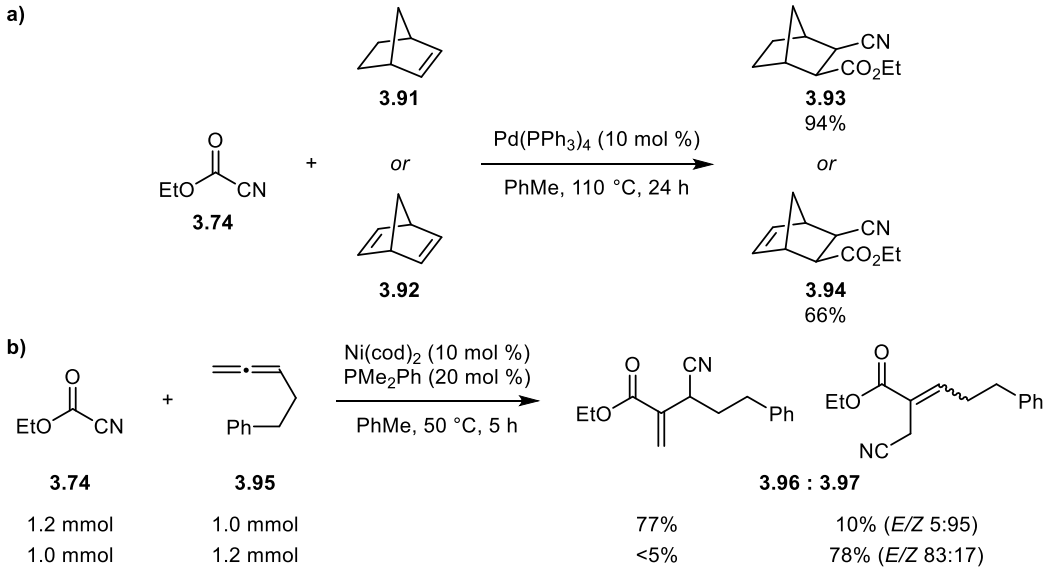
In 2006, Takemoto and coworkers[32–33] developed an intramolecular cyanoamidation reaction. Treatment of aryl- or alkyl-tethered cyanoformamides (**3.87** and **3.89**) with $Pd(PPh_3)_4$ (10 mol %) in xylenes at 130 °C resulted in oxindole **3.88** and γ-lactam **3.89** in 97% and 84% yields, respectively (Scheme 3.21). Oxindole **3.88a** was isolated as a 69:31 mixture of *Z/E* isomers due to isomerization under the reaction conditions. A variety of substituents were tolerated at the alkyne and on the aromatic ring. Furthermore, the tether length of **3.89** could be varied, producing 4-, 6-, and 7-membered lactams (**3.90c–e**) in 23%, 89%, and 79%, respectively.




**Scheme 3.21** Palladium-catalyzed intramolecular cyanoamidation of alkynes

Analogous to carbocyanation, the first intermolecular cyanoamidation of alkenes was performed on norbornenes.[34–36] Nishihara demonstrated that upon treatment with $Pd(PPh_3)_4$ (10 mol %), cyanoformate **3.74** would add across norbornene **3.91** or norbornadiene **3.92** to provide β-nitrile esters **3.93** and **3.94** in 94% and 66% yield, respectively (Scheme 3.22a). When **3.92** was used as the substrate, a second addition of **3.74** was never observed. Other cyanoformates underwent the reaction in moderate to good yields. However, phenyl esters did not provide the desired β-nitrile ester products; instead, diphenyl carbamate was obtained in quantitative yield.

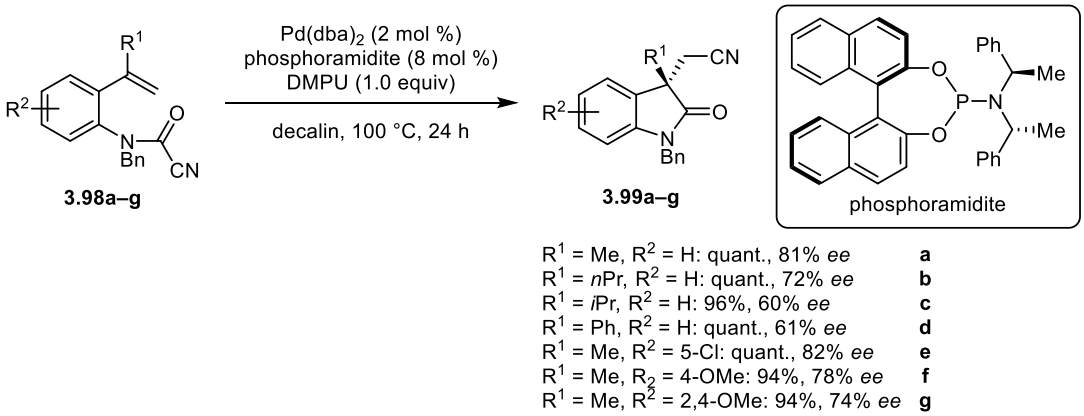
1,2-Dienes were able to serve as alkene surrogates; however, palladium-catalysis was ineffective.[37–38] Instead, reaction of cyanoformate **3.74** with **3.95** in the presence of $Ni(cod)_2$ (10 mol %) and $PMe_2Ph$ (20 mol %) at 50 °C produced a mixture of β-cyanoenoates **3.96** and **3.97** where **3.97** was a 5:95 mixture of *E/Z* isomers (Scheme 3.22b). If the ratio of **3.74** to **3.95** was changed from 1.2:1.0 to 1.0:1.2, the regioselectivity of cyanoesterification switched, producing **3.97** as a 93:17 mixture of *E/Z* isomers with minimal formation of **3.96**. The change in product ratio as well as *E/Z* ratio indicated that reductive elimination was reversible. Indeed, upon subjecting **3.96** to $Ni(cod)_2$ at 100 °C, it isomerized to **3.97**.




**Scheme 3.22** Palladium-catalyzed intermolecular cyanoesterification of alkenes: a) norbornene and norbornadiene; b) 1,2-dienes

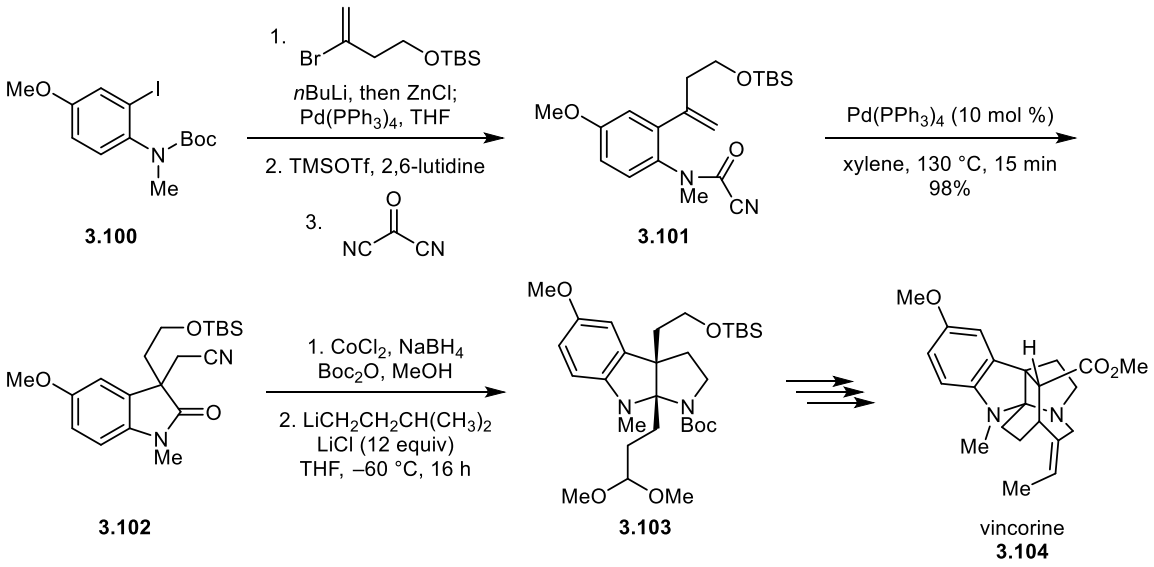
In 2006, Takemoto and coworkers[32–33] continued their investigations into intramolecular cyanoamidation with a report on the cyanoamidation of unactivated alkenes. Using similar conditions to their previous report ($Pd(PPh_3)_4$ in xylene at 130 °C), cyanoformamides were converted to oxindole products. Then, in 2008, they reported an asymmetric variant of this transformation.[39–40] With $Pd(dba)_2$ and BINOL-derived bis[(*R*)-1-phenylethyl]amine phosphoramidite in xylenes at 130 °C, cyanoformamide **3.98a** was converted to oxindole **3.99a** in 96% yield and 69% *ee*. When xylenes was replaced with decalin, higher enantioselectivities were observed (74% *ee*); however, there was incomplete conversion of **3.98a**. When Lewis basic *N*-methyl-2-pyrrolidinone (NMP) was used as the solvent, the reaction went to completion in 15 minutes with a decrease in enantioselectivity (56% *ee*). Using a combination of decalin as the solvent with NMP as a Lewis base additive (1.0 equiv) at 100 °C for 24 hours, afforded **3.98a** in 85% yield and 80% *ee*. Finally, changing the Lewis base to DMPU afforded **3.98a** in quantitative yield and 81% *ee* (Scheme 3.23). The role of DMPU was not studied in detail; additionally, no Lewis acid additives were evaluated. The cyanoamidation reaction

could accommodate substitution at the vinyl group; however, enantioselectivity decreased with increasing bulkiness (Me < *n*Pr < *i*Pr < Ph). Substitution at the aromatic ring did not affect selectivity; however, additional catalyst (5 mol %) and ligand (20 mol %) were required for full conversion of **3.98f**–**g**.




**Scheme 3.23** Palladium-catalyzed intramolecular asymmetric cyanoamidation of alkenes

Takemoto et al.[41] showcased the complexity-building utility of intramolecular cyanoamidation in the synthesis of physostigmine skeleton **3.103**. This pyrroloindole is a core structure for a number of natural products including vincorine (**3.104**). Cyanoformamide **3.101** was prepared by a sequence of Negishi coupling with iodoanisidine (**3.100**), selective deprotection of the *N*-Boc group, and treatment with carbonyl cyanide (Scheme 3.24). Cyanoamidation of **3.101** using $Pd(PPh_3)_4$ (10 mol %) in xylene at 130 °C produced oxindole **3.102** in 98% yield. Selective reduction of the nitrile, protection as the *N*-Boc carbamate, and alkylative cyclization provided the physostigmine core **3.103.**

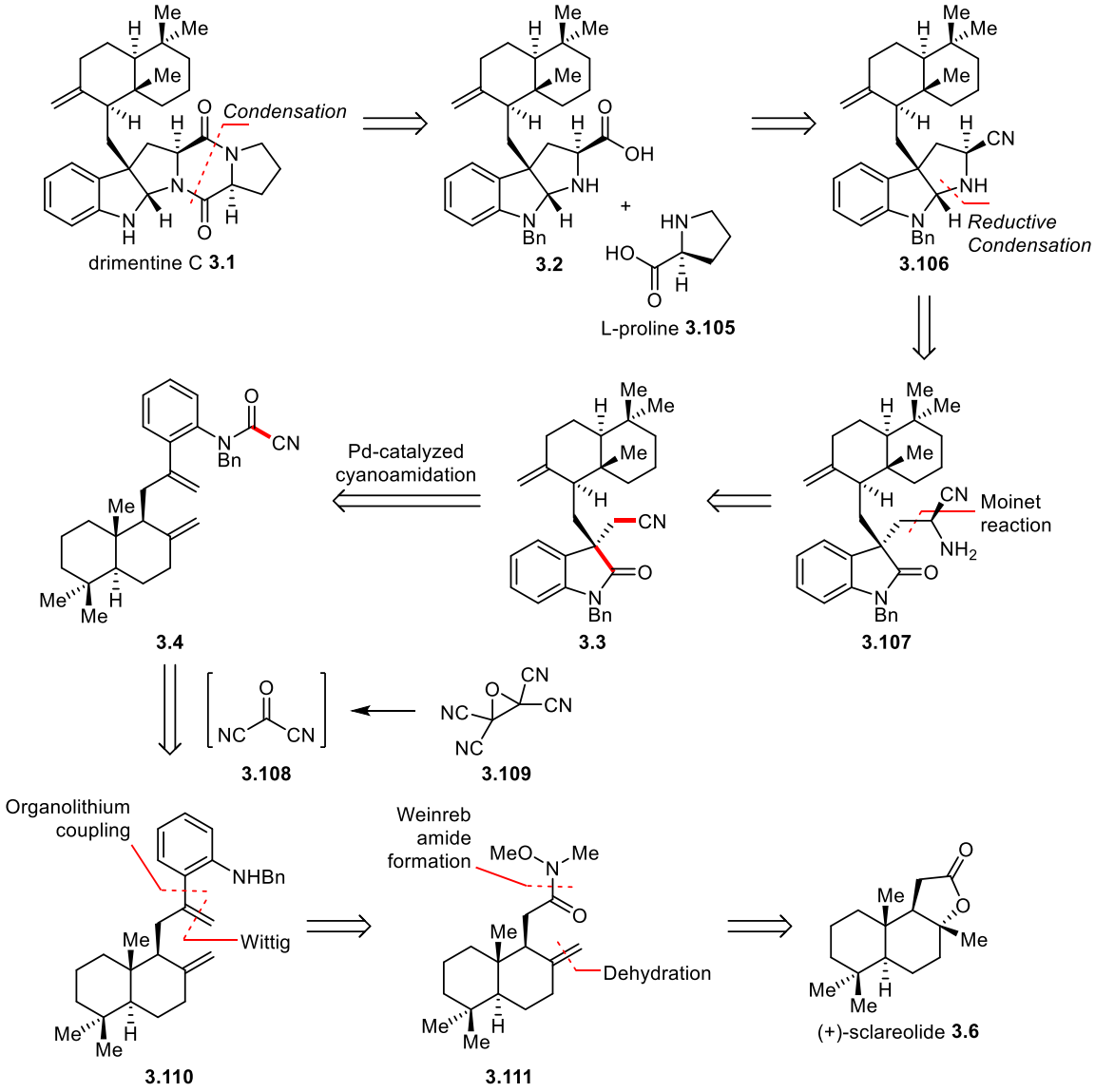



**Scheme 3.24** Synthesis of physostigmine skeleton 3.103 by asymmetric intramolecular cyanoamidation

## 3.3 Synthetic Route to Drimentine C Utilizing Palladium-Catalyzed Cyanoamidation

### 3.3.1 Research Proposal

The ability to set an all-carbon quaternary stereocenter while retaining excellent atom economy makes palladium-catalyzed intramolecular asymmetric cyanoamidation a powerful methodology. We propose that it would allow efficient access to drimentine C (**3.1**). An expanded retrosynthesis is shown in Scheme 3.25.




**Scheme 3.25** Retrosynthetic analysis of drimentine C (3.1) using palladium-catalyzed asymmetric cyanoamidation as the key step

Late-stage formation of the diketopiperazine ring from carboxylic acid **3.2** would allow for diversification to the other family members as the primary difference between the drimentines is the identity of the amino acid condensed within the diketopiperazine. For drimentine C, it would be L-proline (**3.105**). Carboxylic acid **3.2** could be synthesized from nitrile **3.106** via acid-catalyzed hydrolysis.[42] Preparation of the diketopiperazine

ring can be accomplished using a peptide coupling agent, such as HATU or EDC•HCl,[43–45] with **3.2** and **3.105** protected orthogonally as a Boc carbamate and a methyl ester, respectively.

The hexahydropyrrolo[2,3-*b*]indole in **3.106** would be prepared from oxindole **3.3**. First, **3.3** would undergo a Moinet[46] reaction, which involves reduction of the nitrile to an imine followed by nucleophilic addition of cyanide. This sequence has proven successful in the syntheses of anticapsin[47] and (2*S*,3*S*)-ethanolamines.[48] Aminonitrile **3.107** would be closed to pyrroloindoline **3.106** by reductive condensation, a transformation well precedented in the context of total synthesis.[49–55] Conditions would be carefully chosen to avoid reduction of the nitrile.

We envision that oxindole **3.3** could be prepared via palladium-catalyzed intramolecular asymmetric cyanoamidation of cyanoformamide **3.4**. Based on previous work by Takemoto and coworkers[39–40] (Scheme 3.23), we envision the reaction could be run in decalin using $Pd_2(dba)_3$, a chiral phosphoramidite ligand, and added DMPU. To optimize the diastereoselectivity of the cyclization, various ligands and protecting groups would be screened. It is of interest to test the unprotected cyanoformamide as well as testing benzyl- and trityl-protected cyanoformamides, since the steric bulk of the amide substituent has been shown to impact stereoselectivity.[5] The protecting group on the oxindole nitrogen may control the reactivity of the oxindole carbonyl towards organometallic reagents.

Cyanoformamide **3.4** would be prepared from amine **3.110** by nucleophilic addition of carbonyl cyanide (**3.108**), which is prepared *in situ* form tetracyanoethyleneoxide (TCNEO, **3.109**) and dimethyl sulfoxide.[56–59] Ketone **3.110** would be prepared from Weinreb amide **3.11** in a sequence of two steps: nucleophilic addition of the organolithium prepared from lithium-halogen exchange[60–62] of *N*-benzyl-2-iodoaniline and Wittig olefination.[63–64] Weinreb amide **3.111** can be prepared from commercially-available (+)-sclareolide (**3.5**) in two steps, which are detailed in the following section.[65–69]

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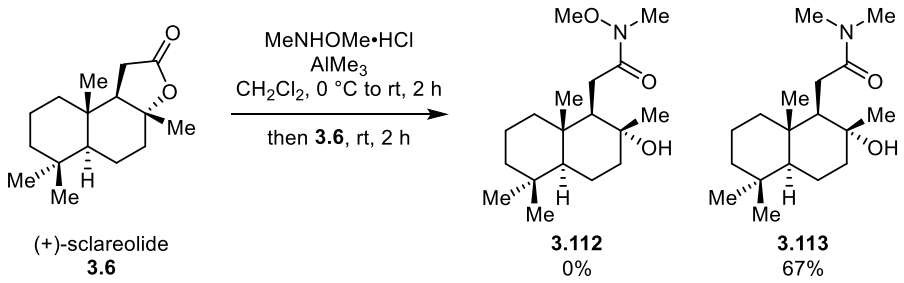
[5] Unpublished work by Prof. Christopher J. Douglas.

### 3.3.2 Progress Towards Key Intermediate 3.4

Preparation of key cyanoformamide intermediate **3.4** began with commercially-available (+)-sclareolide (**3.6**). Following the literature procedure with only a change in the scale (200 mg instead of 2.5 g),[68] we attempted to open the lactone and trap it as Weinreb amide **3.112**. To a stirred solution of *N*-methoxy-*N*-methylamide hydrochloride and $AlMe_3$ in $CH_2Cl_2$ at room temperature was added (+)-sclareolide (Scheme 3.26). The reaction was allowed to proceed for 2 hours then quenched with 10% aqueous $H_2SO_4$ (v/v). A single product was isolated. However, while two new methyl peaks were present in the $^1H$ NMR spectrum of the product, they were significantly upfield from the reported chemical shifts. The molecular formula for the product, $C_{18}H_{33}NO_2$, determined by high-resolution electrospray ionization (ESI) mass spectrometry (MS), corresponded to dimethylamide **3.113**.




**Scheme 3.26** Initial attempt at Weinreb amide formation

In an effort to prepare Weinreb amide **3.112**, several variables were examined. Both the (+)-sclareolide and MeNHOMe•HCl were pure. A new bottle of $AlMe_3$ was obtained and tested under the reaction conditions; however, the reaction reproducibly yielded dimethylamide **3.113** (0.13–0.16 g, 56–67% yield). Finally, aliquots were removed over the reaction time-course and monitored by $^1H$ NMR spectroscopy; the results are shown in Table 3.1. Upon completion of the dropwise addition over 10 minutes of the (+)-sclareolide solution in $CH_2Cl_2$ to the reaction mixture, half of the (+)-sclareolide had already been consumed, and Weinreb amide **3.112** was the only product.

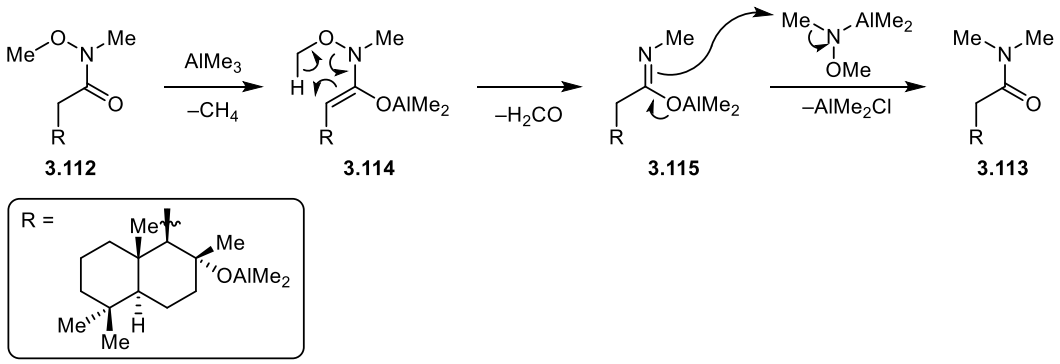
Within 1.5 hours, **3.6** had been fully consumed, and dimethylamide **3.113** was the major product. From this, we determined that dimethylamide **3.113** was the decomposition product of Weinreb amide **3.112**.

**Table 3.1** Distribution of products over time

| Entry | Time (h) | **3.6** : **3.112** : **3.113**[a] |
|---|---|---|
| 1[b] | 0 | 1:1:0 |
| 2 | 0.5 | 11.5:50:1 |
| 3 | 0.7 | 1:7:0 |
| 4 | 1.5 | 0:1:99 |
| 5 | 2.0 | 0:1:99 |
| 6 | 18 | 0:1:142 |

[a] Mole ratio determined by $^{1}$H NMR spectroscopy. [b] After completion of dropwise addition of **3.6** over 10 minutes.

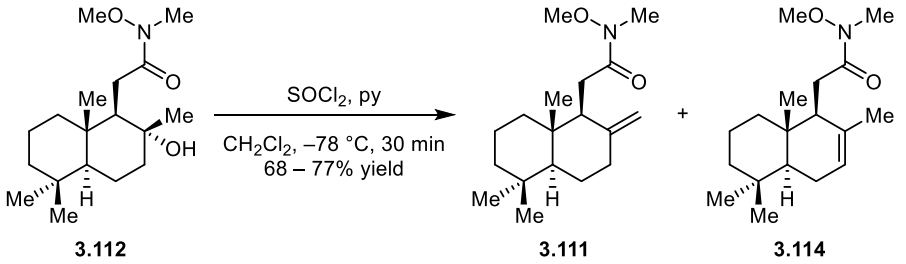
While loss of the methoxy group from Weinreb amides had previously been reported, addition of a methyl group had not.[70–71] Keck and coworkers[72] had observed loss of the methoxy group from multiple Weinreb amides with addition of $CH_2OTBS$ to the nitrogen of the amide. Similar to the mechanism proposed by Keck, we hypothesized that the decomposition of Weinreb amide **3.112** occurs by coordination of $AlMe_3$ to the carbonyl (Scheme 3.27). Loss of the methoxy group occurs via a retro-ene reaction to produce imine **3.115** and formaldehyde. A methyl group is obtained from a reactive species in solution to yield dimethylamide **3.113.**




**Scheme 3.27** Proposed mechanism for formation of dimethylamide **3.113**

Having determined that dimethylamide **3.113** was the decomposition product of Weinreb amide **3.112**, the timing of the reaction was optimized. On a 200 mg scale, the optimal reaction time was 1.25 hours. When using 2.5 g of (+)-sclareolide, the reaction conditions as reported in the literature procedure[68] were optimal, providing Weinreb amide **3.112** in 65% yield (average, 38–81%) after purification by column chromatography.

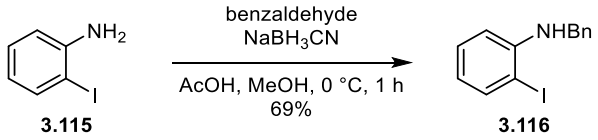
Selective dehydration of the tertiary alcohol in Weinreb amide **3.112** to the exocyclic olefin was performed according to the literature procedure.[68] A solution of thionyl chloride and pyridine in $CH_2Cl_2$ was added dropwise to a solution of Weinreb amide **3.112** in $CH_2Cl_2$ at –78 °C. After 30 minutes, the reaction was quenched with either saturated aqueous $NaHCO_3$ or a saturated solution of $NaHCO_3$ in MeOH. While the reaction proceeded quickly, isolation of the product was challenging. The excess pyridine was difficult to remove by column chromatography. This problem was solved by adding an extraction with 0.2 M aq. $CuSO_4$ to the workup procedure. Overall, the dehydration reaction provided **3.111** with its endocyclic $\Delta^{7,8}$-isomer **3.114** in a 5:1 mixture. Careful chromatography (using $AgNO_3$-impregnated silica gel, silica gel with a smaller particle size, or a long, wide column with regular silica gel) allowed for the isolation of **3.111** in 67% yield (average, 48–87%).




**3.112** **3.111** **3.114**

**Scheme 3.28** Elimination of Weinreb amide **3.112** to exocyclic olefin **3.111**

The next step in the synthesis was addition of the aniline moiety to Weinreb amide **3.111**. However, first the nitrogen atom of 2-iodoaniline **3.115** was protected (Scheme 3.29). Choice of this protecting group was important as it would have an effect on the diastereoselectivity of the palladium-catalyzed asymmetric cyanoamidation reaction. Previously, substrates with a benzyl protecting group yielded the corresponding oxindole products in up to 81% *ee* (Scheme 3.23);[39–40] therefore, benzyl was the first choice for protection of **3.115**. Reductive amination of **3.115** was performed by stirring with benzaldehyde, sodium cyanoborohydride, and acetic acid in MeOH at 0 °C for 1 hour. Purification by column chromatography provided **3.116** in 69% yield.

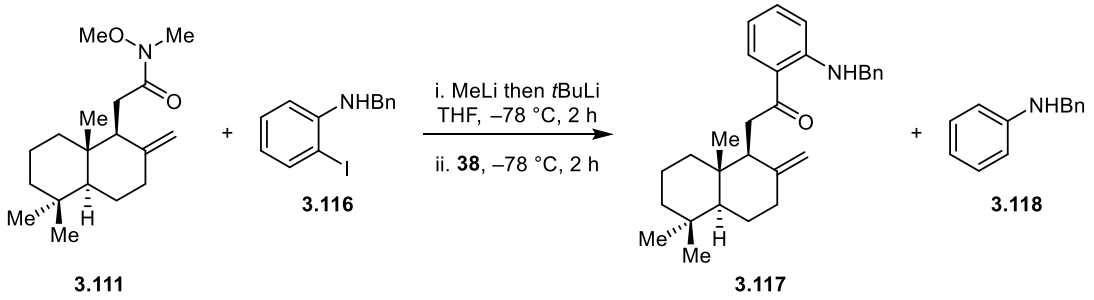



**3.115** **3.116**

**Scheme 3.29** Reductive amination of 2-iodoaniline **3.115**

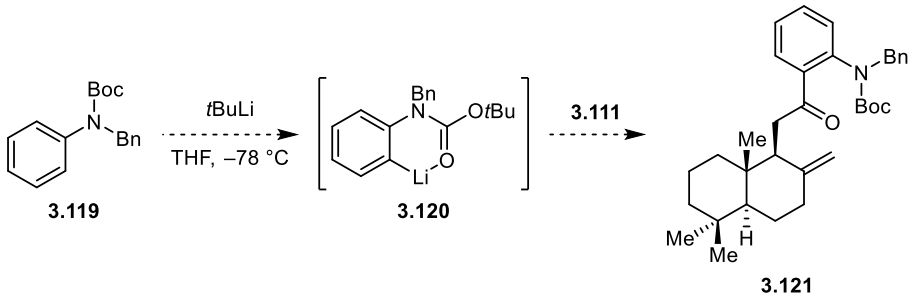
*N*-benzyl-2-iodoaniline **3.116** was subjected to lithium-halogen exchange wherein **3.116** was deprotonated with one equivalent of methyl lithium at –78 °C then treated with *tert*-butyl lithium. Addition of Weinreb amide **3.111** was predicted to provide ketone **3.117** by nucleophilic addition (Scheme 3.30). While the $^{1}$H NMR spectrum of the crude reaction mixture showed some evidence of desired product **3.117**, isolation from byproduct **3.118** was challenging. Furthermore, the results were not reproducible. When the reaction was run a second time, only Weinreb amide **3.111** and *N*-benzylaniline **3.118**

were isolated from the reaction; no formation of **3.117** was observed.




**Scheme 3.30** Initial attempt at organolithium coupling

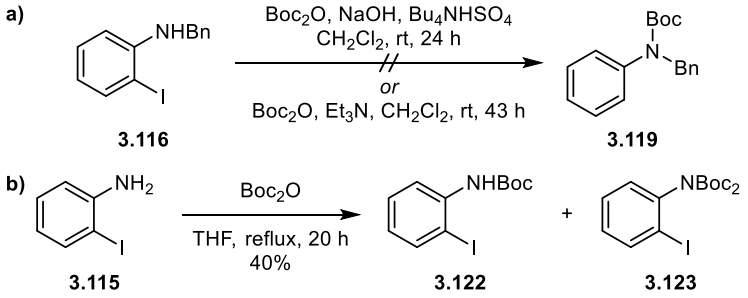
Reported organolithium additions of anilines to Weinreb amides had the nitrogen protected with carbonyl-containing protecting groups, like carbamates.[60–62] The carbonyl stabilized the organolithium via chelation. Therefore, we predicted that using di-protected aniline **3.119** (Scheme 3.31) would improve the organolithium addition to Weinreb amide **3.111**. Not only would the *N*-Boc group assist via chelation (intermediate **3.120**), but also the deprotonation with methyl lithium would no longer be necessary.




**Scheme 3.31** Proposed organolithium coupling using chelation assistance

Benzyl-protected **3.116** was treated with $Boc_2O$ (2.0 equiv), sodium hydride, and $Bu_4NHSO_4$ in $CH_2Cl_2$ at room temperature for 24 hours (Scheme 3.32a); however, only **3.116** was recovered (80% recovery). Treatment of **3.116** with $Boc_2O$ (1.1 equiv) and triethylamine in $CH_2Cl_2$ at room temperature for 43 hours was similarly unsuccessful.

Finally, the order of protections was reversed. 2-Iodoaniline **3.115** was refluxed with $Boc_2O$ in THF for 20 hours (Scheme 3.32b). However, this produced an inseparable mixture of mono-protected **3.122** and di-protected **3.133** in 40% yield. At this point, the route was abandoned in favor of the convergent route discussed in Chapter 4.




**Scheme 3.32** Attempted *N*-Boc protections: a) attempted preparation of **3.119**; b) *N*-Boc protection of **3.115**

## 3.4 Concluding Remarks

Chapter 3 has discussed the background, proposed synthesis, and progress towards the total synthesis of drimentine C (**3.1**) via a linear route using palladium-catalyzed asymmetric cyanoamidation as the key step. Ultimately, with the continued reports of newly isolated drimentines as well as the challenges in the synthesis of key intermediate, cyanoformamide **3.4**, this route was abandoned in favor more convergent routes.

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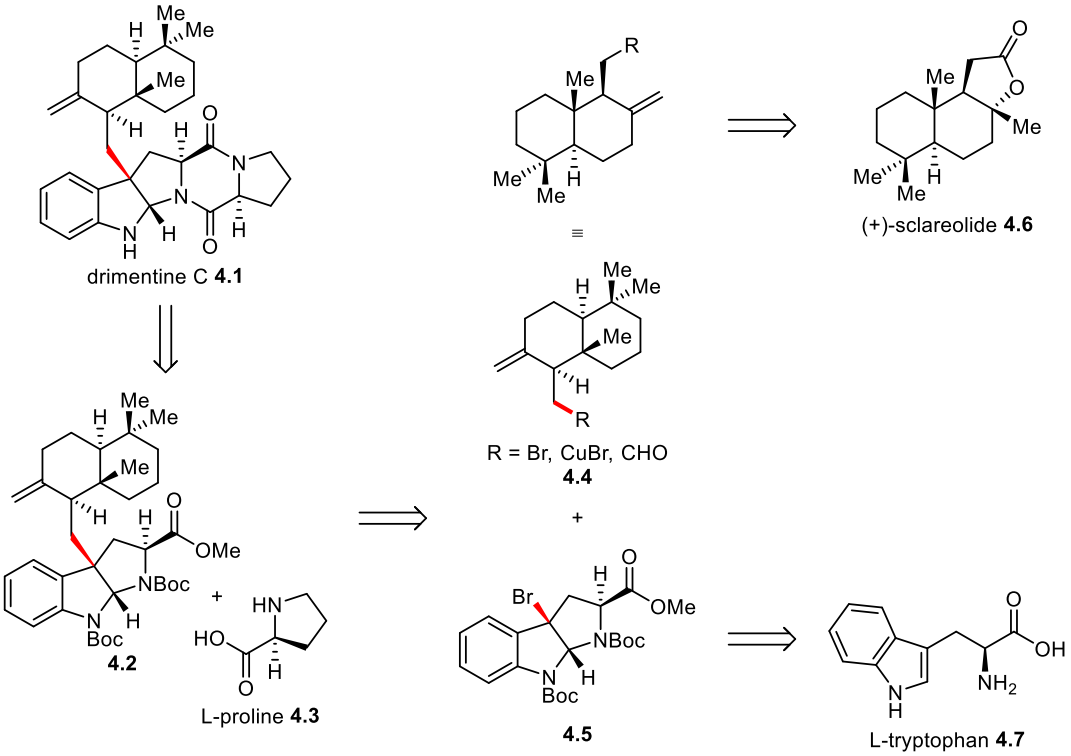
# Chapter 4: Progress Toward a Total Synthesis of Drimentine C via a Convergent Route

## 4.1 Introduction

In the interest of assembling drimentine C (**4.1**) most efficiently, we decided to attempt a highly convergent route (Scheme 4.1). We would take advantage of the stereocenters already present in nature by utilizing L-proline (**4.3**), (+)-sclareolide (**4.6**), and L-tryptophan (**4.7**) as starting materials. This would provide us with all of the necessary carbons—with one additional—as well as five of the seven stereocenters in the proper configurations.

One goal of this synthetic route was to maintain those stereocenters. Another goal, learned from the experience of Li et al.[1] in their total synthesis of drimentines A, F, and G, was to establish the exocyclic olefin early in the synthesis. In order to accomplish the proposed route, we needed to develop a method for the coupling of key intermediates **4.4** and **4.5** to give pyrroloindoline **4.2**. This chapter will detail the search for a method that would make the desired C–C bond.




**Scheme 4.1** Proposed retrosynthesis of drimentine C (4.1) by a convergent route

## 4.2 First Generation Synthetic Route to Drimentine C

Because bromopyrroloindoline **4.5** serves as the linchpin to the convergent synthesis of drimentine C (**4.1**), the stereochemical issues regarding its synthesis and C3a-alkylation will be discussed. In this section, the atom numbering used is that for the base hexahydropyrrolo[2,3-*b*]indole core as shown in Figure 4.1. Additionally, hexahydropyrrolo[2,3-*b*]indole will be abbreviated to pyrroloindoline. After the background on bromopyrroloindoline **4.5**, our first proposal, an organocuprate addition into cyclopropylazetoindoline **4.9**, will be presented and analyzed.

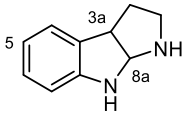
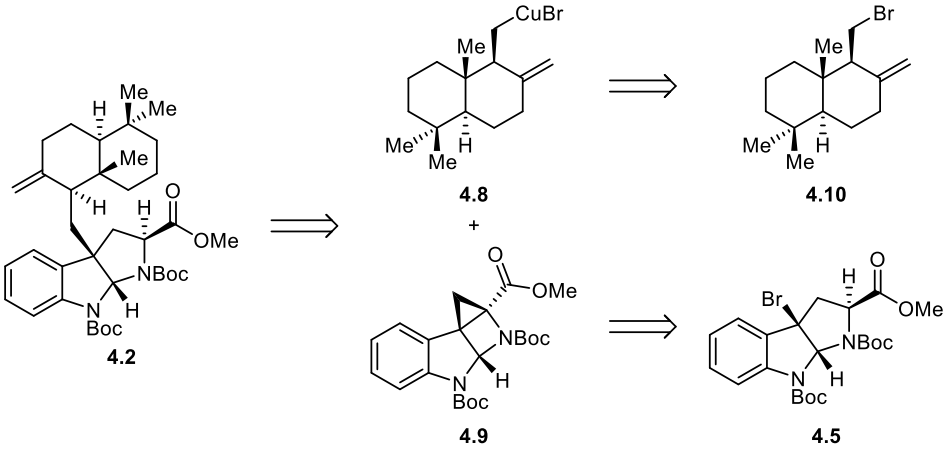


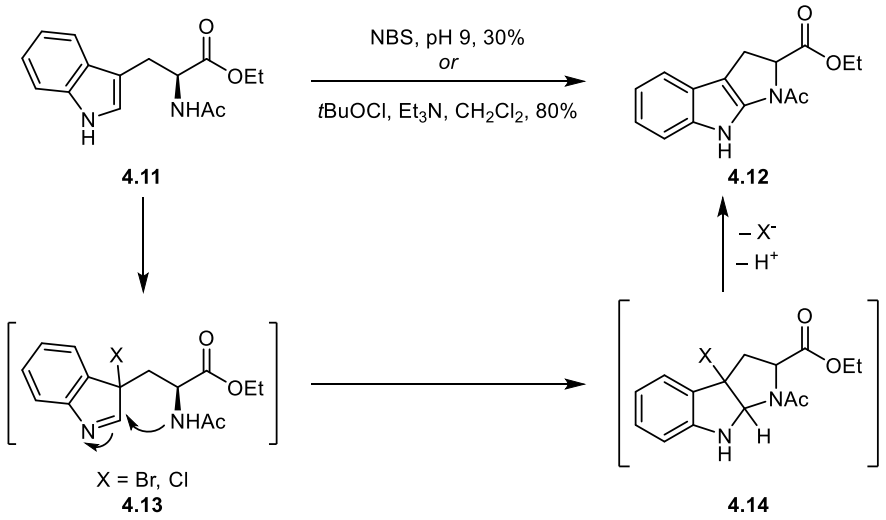

**Figure 4.1** Hexahydropyrrolo[2,3-b]indole core




**Scheme 4.2** First generation proposal for coupling to product **4.2**

### 4.2.1 Background on the Preparation of Cyclic Tryptophan Derivatives

In 1970, Witkop et al.[2] reported the first preparation of 2,3-dihydro[2,3-*b*]indole **4.12** from a tryptophan derivative, **4.11**, in a single step—an oxidative cyclization. Treatment of **4.11** with either *N*-bromosuccinimide (NBS) at pH 9 or *tert*-butyl-hypochlorite and triethylamine in dichloromethane provided **4.12** in 30% and 80% yields, respectively (Scheme 4.3). Witkop proposed that 3-haloindolenine **4.13** formed first, followed by ring closure to 3-haloindoline **4.14**. Consecutive loss of the halide and a proton would accomplish rearomatization of the system providing observed product **4.12**. The final stereochemistry of the ethyl ester was not determined.



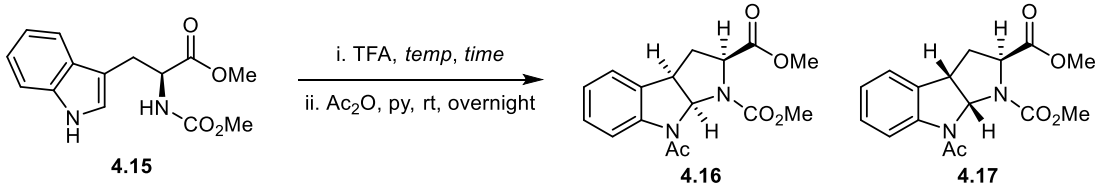

**Scheme 4.3** Preparation of 2,3-dihydro[2,3-b]indole **4.12**

Following the work of Witkop, Hino and coworkers[3] carried out a series of studies on the cyclic tautomers of tryptophan derivatives. They found that tryptophan derivative **4.15** underwent cyclization to the corresponding pyrroloindolines upon treatment with a variety of acids (aqueous phosphoric acid (85%), aqueous sulfuric acid (75–85%), sulfuric acid in methanol (50–85%), and trifluoroacetic acid). Immediate acetylation of the resulting pyrroloindolines yielded mixtures of **4.16** and **4.17**. Because the methyl ester of **4.16** is on the concave face of the fused ring system, it is termed the *endo*-isomer. Analogously, **4.17** is the *exo*-isomer because the methyl ester is on the convex face of the ring system. This terminology will be used throughout the chapter and always refers to the orientation of the carbonyl group at C2 relative to the pyrroloindoline ring fusion.

When aqueous phosphoric acid (85%) was used for the oxidative cyclization, *endo*-**4.16** was the sole product. *Exo*-**4.17** was detected by $^{1}$H NMR spectroscopy when aqueous sulfuric acid (70%) was used; however, it could not be isolated because it quickly reverted to **4.15**. A screening of reaction times and temperatures revealed that *endo*-**4.16** was the thermodynamically-preferred product, while *exo*-**4.17** was less stable but kinetically favored. At longer reaction times (Table 4.1, entry 2), **4.16** predominated;

however, at short reaction times (entry 3) or low temperatures (entry 4), **4.17** was the major product. Subsequent NMR spectroscopic and X-ray crystallographic studies done by Crich et al.[6] determined that the thermodynamic preference for the *endo*-isomer is a function of torsional interactions around the bicyclo[3.3.0]octane core. In particular, the *endo*-isomer is able to achieve an envelope conformation while the *exo*-isomer cannot; it exists as an imperfect half-chair where a portion of the ester (either the C–C bond or the C=O bond) eclipses the N1–C2 bond.

**Table 4.1** Acid-catalyzed oxidative cyclization of **4.15** to *endo*-**4.16** and *exo*-**4.17**

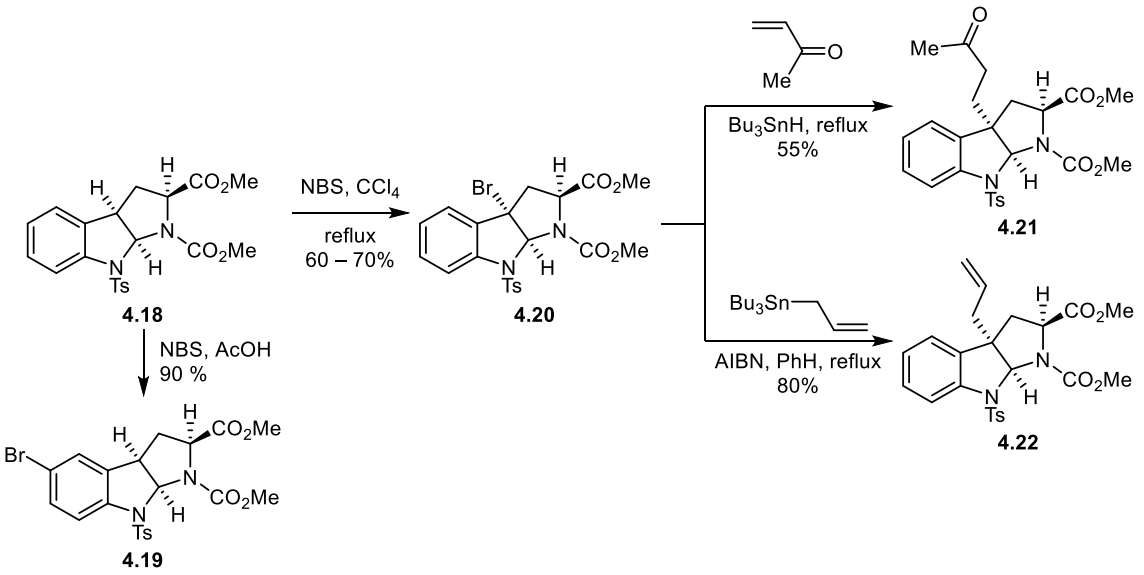



**4.15** **4.16** **4.17**

| Entry | Temp (°C) | Time (min) | **4.16 : 4.17** |
|---|---|---|---|
| 1 | 15 | 30 | 1 : 1.1 |
| 2 | 16 | 60 | 4.3 : 1 |
| 3 | 15 | 2–3 | 1 : 20 |
| 4 | –18 to –10 | 30 | 1 : 10 |

Crich and coworkers[4–8] also undertook a series of studies on the reactivity and selectivity of pyrroloindolines prepared from L-tryptophan derivatives. In 1994, they found that *endo*-**4.18** could be selectively brominated.[5] When treated with NBS in acetic acid, **4.18** underwent bromination at C5 providing **4.19** in 90% yield (Scheme 4.4). However, when the acid was removed and the reaction was conducted with NBS in refluxing chloroform, benzylic bromination at the C3a-position occurred. *Endo*-bromopyrroloindoline **4.20** was obtained in 60–70% yield. Unlike the dehydration of **4.14** to **4.12** observed by Witkop,[2] **4.20** was stable to silica gel chromatography as well as standing in air for several months. Bromopyrroloindoline **4.20** underwent conjugate addition when treated with tributyltin hydride and methyl vinyl ketone to provide *endo*-

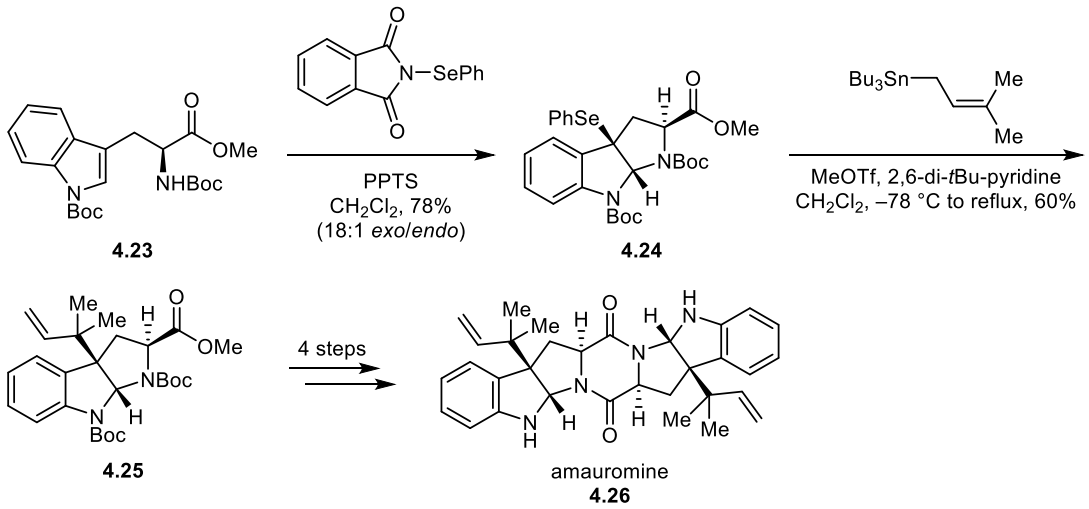
**4.21** in 55% yield. Radical reaction between **4.20** and allyltributyltin using AIBN as the initiator provided **4.22** in 80% yield.




**Scheme 4.4** C3a-bromination of pyrroloindoline **4.18** and subsequent alkylation

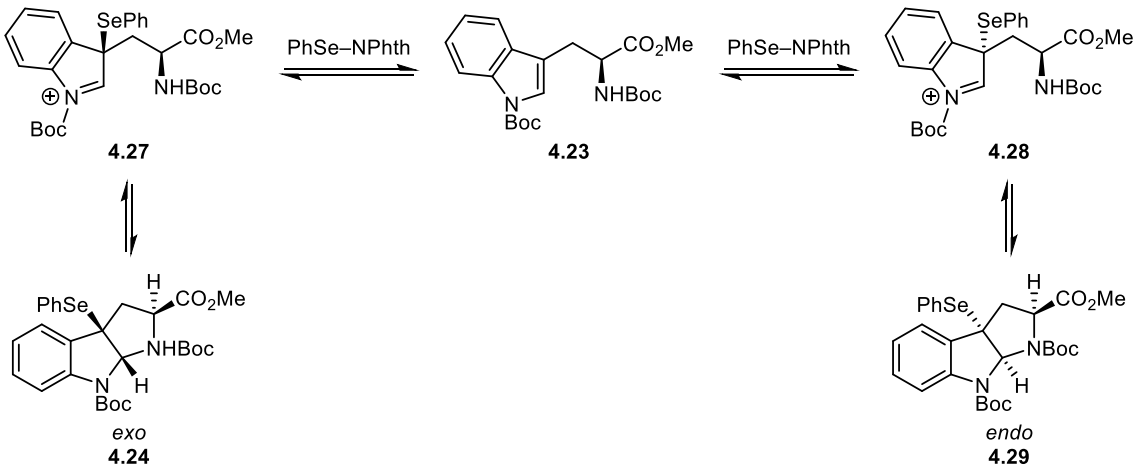
In 1994, Danishefsky and coworkers[9] reported that tryptophan derivative **4.23** underwent phenylselenation with *N*-phenylselenophthalimide and catalytic *p*-toluenesulfonic acid (PTSA) providing pyrroloindoline **4.24** as a 9:1 mixture of diastereomers in 78% yield favoring *exo*-**4.24**. By switching from PTSA to anhydrous pyridinium *p*-toluenesulfonate (PPTS), they improved the yield and selectivity of the phenylselenation attaining **4.24** in 93% yield as an 18:1 (*exo/endo*) mixture of diastereomers (Scheme 4.5). Treatment of **4.24** with methyl triflate and prenyl tributylstannane in the presence of 2,6-di-*t*Bu-pyridine conducted reductive cleavage of the phenylseleno group and reverse prenylation at C3a to provide **4.25** in 60% yield as an unchanged mixture of diastereomers. They used pyrroloindoline **4.25** as a key intermediate in their total synthesis of amauromine (**4.26**). This was the first example of an oxidative cyclization of an L-tryptophan derivative preferentially forming the *exo*-diasteromer. Additionally, the stereochemical information was maintained throughout the

radical-mediated C3a-alkylation presumably due to the strong preference for a *cis*-ring fusion of the interlocked 5,5-ring system.




**Scheme 4.5** Phenylselenation of **4.23** to prepare *exo*-**4.24** and use in total synthesis of amauromine (**4.26**)

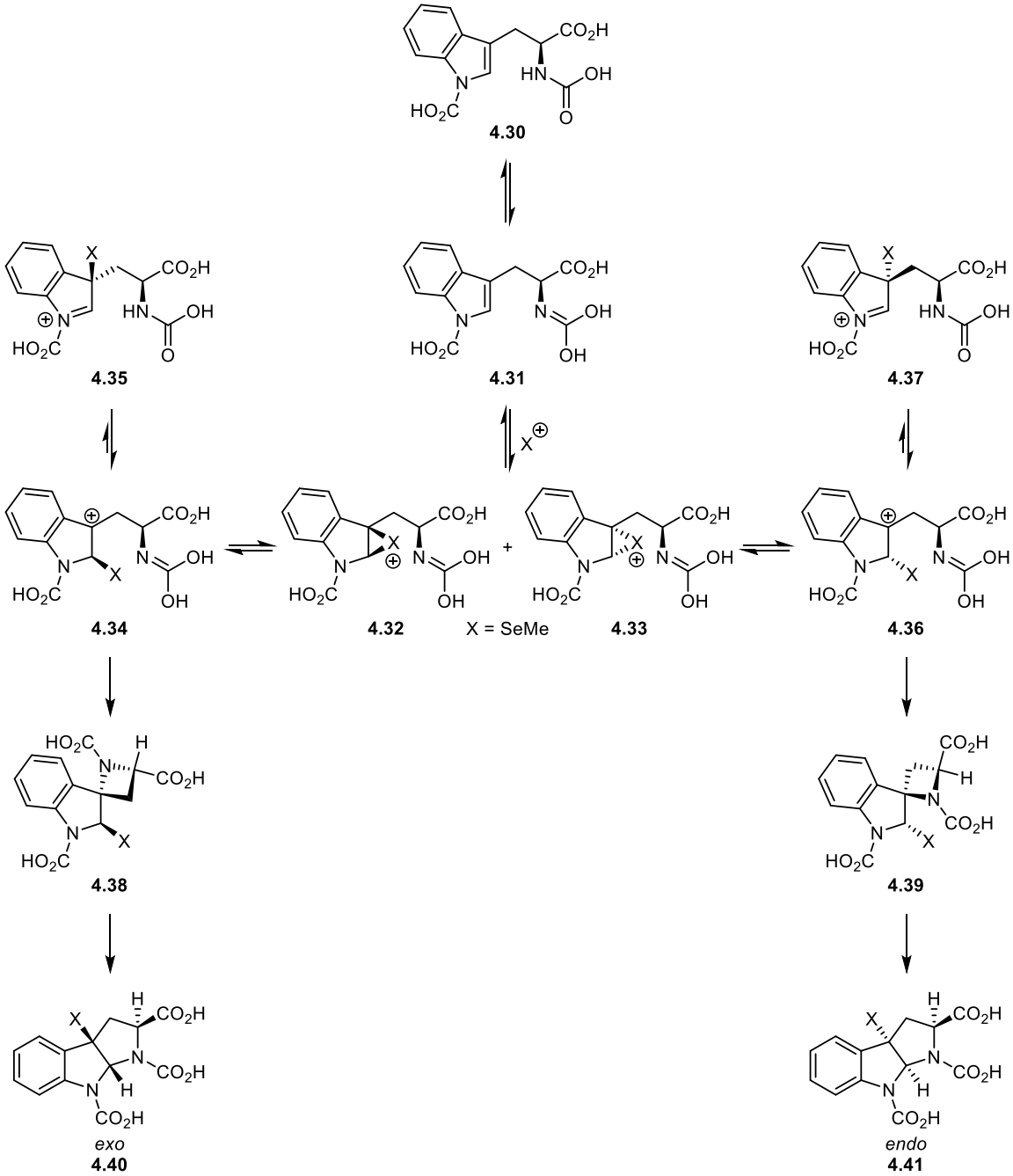
One mechanistic proposal for the phenylselenocyclization reaction was proposed by Crich et al.[6] Electrophilic addition to the indole would provide indolenium ions **4.27** and **4.28**. They proposed that these were in rapid equilibrium because it seemed unlikely that a single stereocenter two freely-rotating bonds away would provide the level of stereocontrol observed. Instead, they proposed that ring closure to the pyrroloindoline was the stereodetermining step. Ring closure to **4.24** must be faster than that to **4.29** and have an early transition state because a late, product-like transition state would result in a kinetic preference for **4.29**.




**Scheme 4.6** Phenylselenocyclization mechanism proposed by Crich et al.[8]

This mechanism was studied by de Lera et al.[10] using DFT calculations[††] of the model system: **4.30** and $MeSe^+$. The first step is acid-catalyzed keto-enol tautomerization of the carbamate from **4.30** to **4.31** (Scheme 4.7). In the keto-tautomer, the lone pair of the nitrogen is compromised due to its conjugation with the carbonyl group and, therefore, lacks the nucleophilicity required for effective attack. However, when in the enol-tautomer, the nucleophilicity of the nitrogen is enhanced because it is isolated from the carbonyl of the carbamate. Electrophilic selenium activates indole **4.31** through the formation of halonium ions **4.32** and **4.33**, which subsequently open at either C2 or C3 of the indole to produce benzylic carbenium ions **4.34** and **4.36** or iminium ions **4.35** and **4.37**, respectively. Activation of the indole occurs with neither facial nor positional selectivity, so these four species are in a dynamic equilibrium. However, only benzylic carbenium ions **4.34** and **4.36** were found to be productive.

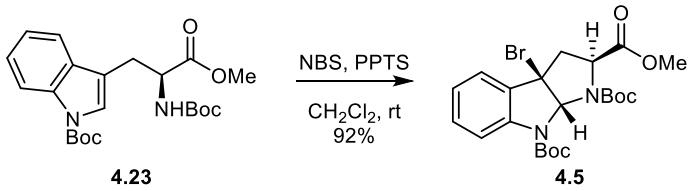
[††] Geometry optimizations and frequency calculations were performed with the B3LYP functional. LANLDZ ECP and its associated basis functions were used for Se and Br with the 6-31G(d) basis set used for the remaining atoms. Solvent effects were included using the PCM model with $CH_2Cl_2$ parameters. Long-range dispersion interactions were included using an energy refinement step with the double hybrid B2PLYP functional in conjunction with a basis set of triple-ζ quality with polarization functions (TZVP) for all atoms.




**Scheme 4.7** Phenylselenocyclization mechanism as determined by DFT calculations

The carbamate nitrogen attacks the carbenium ions to produce spirocyclic azetidine intermediates **4.38** and **4.39**. This is the rate-determining step with an activation

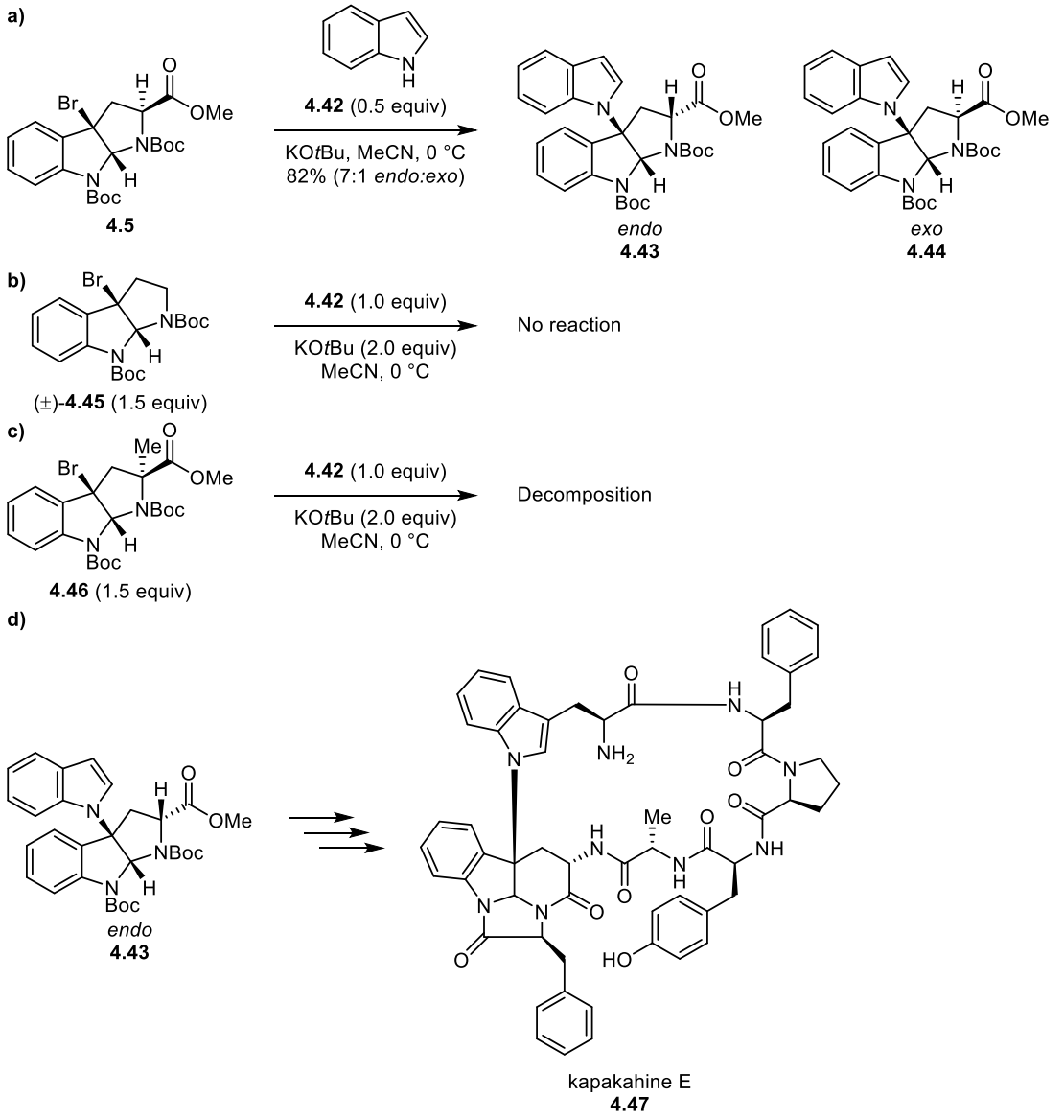
barrier of ~23 kcal $mol^{-1}$. There is an ~1 kcal $mol^{-1}$ difference between the activation energies favoring **4.38**, which is the source of the *exo/endo* selectivity. Surprisingly, there are no obvious structural features responsible for the difference in activation energies as both transition states exhibit similar geometries. Additionally, in the gas phase, there is only ~0.5 kcal $mol^{-1}$ difference between **4.38** and **4.39**—half of the activation energy difference is due to solvation effects! To produce the final pyrroloindolines **4.40** and **4.41**, azetidines **4.36** and **4.37** undergo concerted rearrangement of the nitrogen and selenium atoms. Ring expansion is probably the driving force for this rearrangement. This mechanistic proposal was consistent with the bromocyclization of tryptophan derivatives using NBS and PPTS (Scheme 4.8).




**4.23** **4.5**

**Scheme 4.8** Electrophilic bromocyclization of tryptophan derivatives

In 2008, Rainier and Espejo[11] reported that *exo*-bromopyrroloindoline **4.5** was a suitable substrate for anionic coupling reactions. In particular, reaction of **4.5** with indole **4.42** and sodium hydride in the presence of catalytic silver nitrate produced *endo*-**4.43** as a single diastereomer in 28% yield. Further optimization indicated that silver nitrate was not necessary for reactivity. Additionally, when HMPA or HMPA-DMF (1:5) was used as the solvent, the yield increased (63% and 59%, respectively) but at the expense of selectivity (3:1 and 4:1 *endo/exo*, respectively). The optimal conditions used potassium *tert*-butoxide as the base in MeCN at 0 °C, which provided **4.43** in 82% yield as a 7:1 mixture of diastereomers (**4.43:4.44**) (Scheme 4.9a).

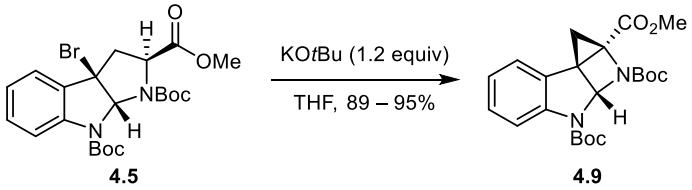



**Scheme 4.9** Reactions of bromopyrroloindolines: a) C3a heterodimeric indoline formation; b) attempted reaction of tryptamine derivative (±)-**4.45**; c) attempted reaction of non-enolizable **4.46**; d) use of **4.43** in total synthesis of kapakahine E

The presence of the ester was essential for reactivity. When **4.45** was subjected to the reaction conditions, only starting material was recovered (Scheme 4.9b). Additionally, the ester needed to be enolizable. When C2-methylated **4.46** was treated

with **4.42** and potassium *tert*-butoxide in MeCN at 0 °C, only unreacted starting material and decomposition products were observed (Scheme 4.9c). This transformation was used in the total synthesis of kapakahine E (Scheme 4.9d).[12]

From the observations using (±)-**4.45** and **4.46** as substrates, Rainier and Espejo[13] proposed that a transiently-formed cyclopropane may assist with loss of bromide. This cyclopropane intermediate, namely cyclopropylazetoindoline **4.9**, could in fact be isolated and was stable when stored at 0 °C for several weeks. Reaction of **4.5** with potassium *tert*-butoxide in THF in the absence of any nucleophile provided **4.9** in 89–95% yield (Scheme 4.10).

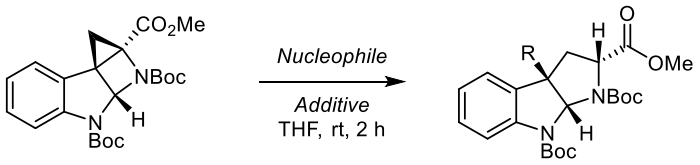



**4.5** **4.9**

**Scheme 4.10** Preparation of cyclopropylazetoindoline **4.9**

Isolated cyclopropylazetoindoline **4.9** could be reacted with a variety of nucleophiles to provide *endo*-products **4.48a–h** in good yields (Table 4.2). The nucleophiles included inorganic salts (entries 1 and 2), phenols and thiophenols (entries 3 and 4), C–H acids (entries 5 and 6), and carbon nucleophiles (entries 7 and 8). Of note, bromopyrroloindoline **4.5** was inert to these transformations.

**Table 4.2** Reactions of cyclopropylazetoindoline **4.9** with various nucleophiles




**4.9** **4.48a–h**

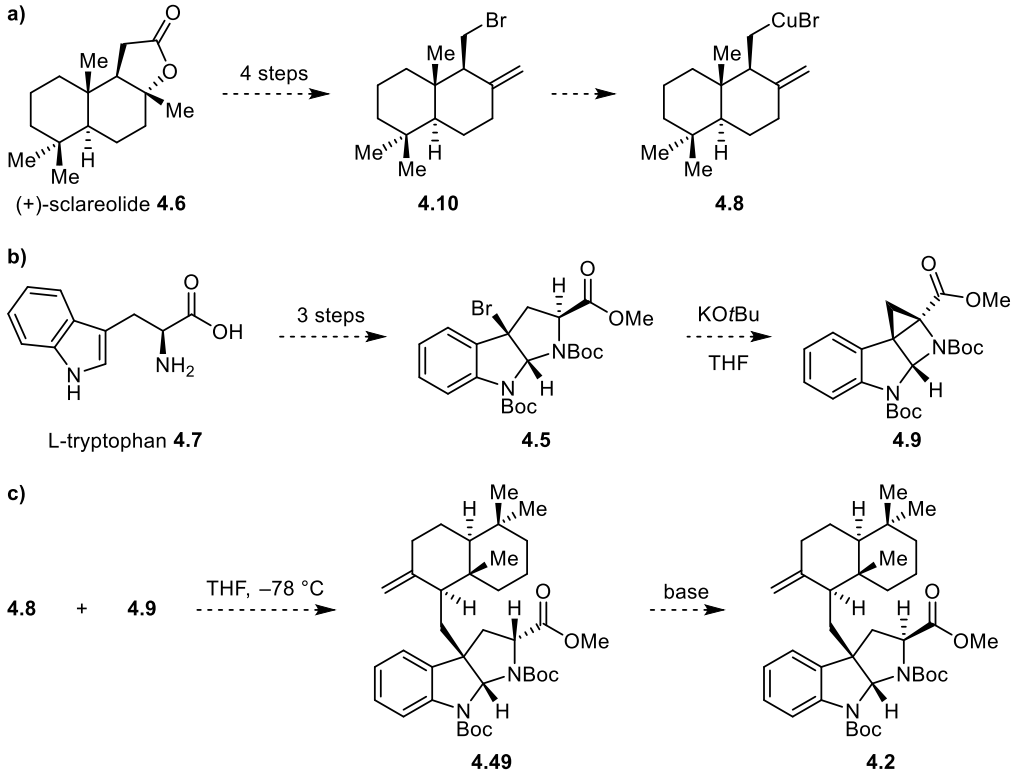
| Entry | Nucleophile (equiv) | Additive | R | Product | Yield (%) |
|---|---|---|---|---|---|
| 1 | $NaBH_4$ (10) | none | H | **4.48a** | 75 |
| 2 | KCN (10) | PPTS, 18-crown-6[a] | CN | **4.48b** | 70 |
| 3 | PhOH (5) | PPTS[b] | OPh | **4.48c** | 72 |
| 4 | PhSH (5) | DBU[c] | SPh | **4.48d** | 84 |
| 5 | $MeNO_2$ (10) | DBU | $CH_2NO_2$ | **4.48e** | 50 |
| 6 | $CNCH_2CN$ (10) | DBU | $CH(CN)_2$ | **4.48f** | 60 |
| 7 | $AlMe_3$ | none[d] | Me | **4.48g** | 76 |
| 8 | *p*-Me-PhMgBr, CuCN (5) | none[e] | *p*-MePh | **4.48h** | 70 |

[a] Reaction time: 4 h. [b] Used DMF instead of THF. [c] Reaction time: 5 h. [d] Reaction conducted in $CH_2Cl_2$ from –40 to 0 °C over 0.5 h. [e] Reaction conducted at –78 °C for 15 min.

### 4.2.2 Research Proposal: Organocuprate Addition to Cyclopropylazetoindoline 4.9

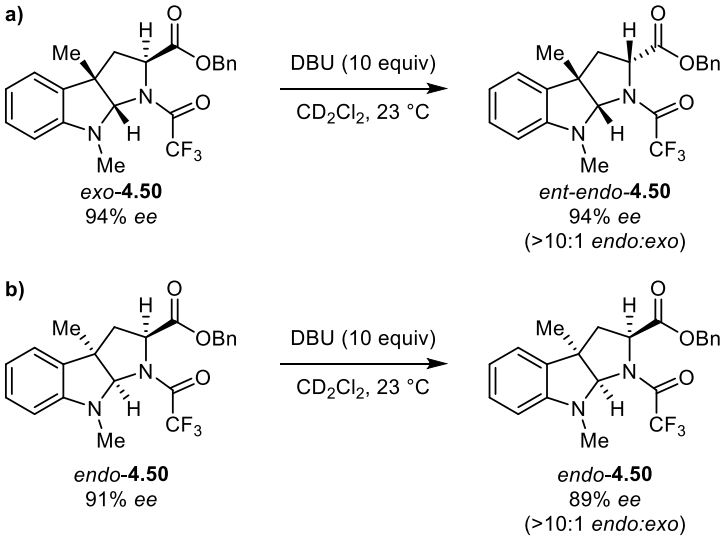
We proposed that (+)-sclareolide (**4.6**) could be transformed into bromide **4.10** in four steps (Scheme 4.11a). Preparation of organocuprate **4.8** from bromide **4.10** would provide the first key coupling partner. L-Tryptophan can be converted to bromopyrroloindoline **4.5** in three steps (Scheme 4.11b). Conversion of **4.5** into cyclopropylazetoindoline **4.9** using the conditions of Rainier and Espejo[13] would provide the second coupling partner. Organocuprate addition into **4.9** would result in *endo*-**4.49** (Scheme 4.11c). Treatment with base would favor *endo*-**4.49**; however, it may be possible to optimize the conditions (potassium *tert*-butoxide[7] or HMPA[11]) such that the

desired *exo*-isomer **4.2** is also produced.




**Scheme 4.11** Proposed construction of the drimentine core using an organocuprate addition to cyclopropylazetoindoline **4.9**

However, studies reported by Reisman et al.[14] in 2010 indicated that the proposed epimerization was unlikely to be successful. When *exo*-**4.50** was treated with DBU, it returned the *endo*-isomer in identical enantioselectivity (94% *ee*) (Scheme 4.12a). If *endo*-**4.50** was treated with DBU, only a slight erosion of enantioselectivity (91% *ee* to 89% *ee*) was detected (Scheme 4.12b).



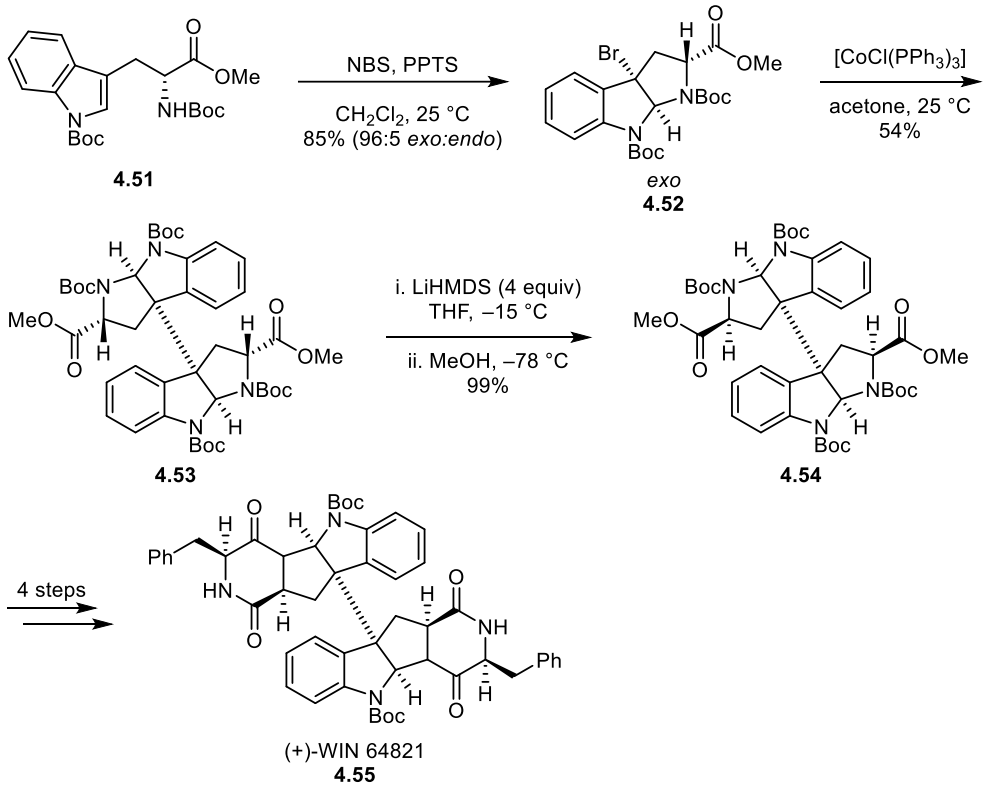

**Scheme 4.12** Pyrroloindoline epimerization studies

While the above synthetic proposal would construct the drimentine core quickly, **4.49** would have the incorrect stereochemistry at the methyl ester. Base-catalyzed epimerization would at best provide mixtures of **4.49** and **4.2**. So, we decided to abandon this methodology for construction of the drimentine core in favor of one that would not affect the C2 stereocenter.

## 4.3 Second Generation Synthetic Route to Drimentine C

Turning to the pyrroloindoline alkaloid literature, we found that a possible solution to the problem of C2-epimerization during the C3a bond-forming step was to use a radical-based methodology. This would have the benefit of maintaining the favorable 5,5-*cis* ring fusion while leaving the other stereocenters untouched. In fact, radical-based methodologies have proven useful for the synthesis of pyrroloindoline homodimers.[15] One notable example is the total synthesis of (+)-WIN 64821 (**4.55**) by de Lera et al.[16] They prepared *exo*-bromopyrroloindoline **4.52** in 85% yield with a 95:5 dr from D-tryptophan derivative **4.51** using NBS and PPTS. Bromopyrroloindoline **4.52** was subjected to $[CoCl(PPh_3)_3]$ in acetone at 25 °C, which initiated the radical-mediated

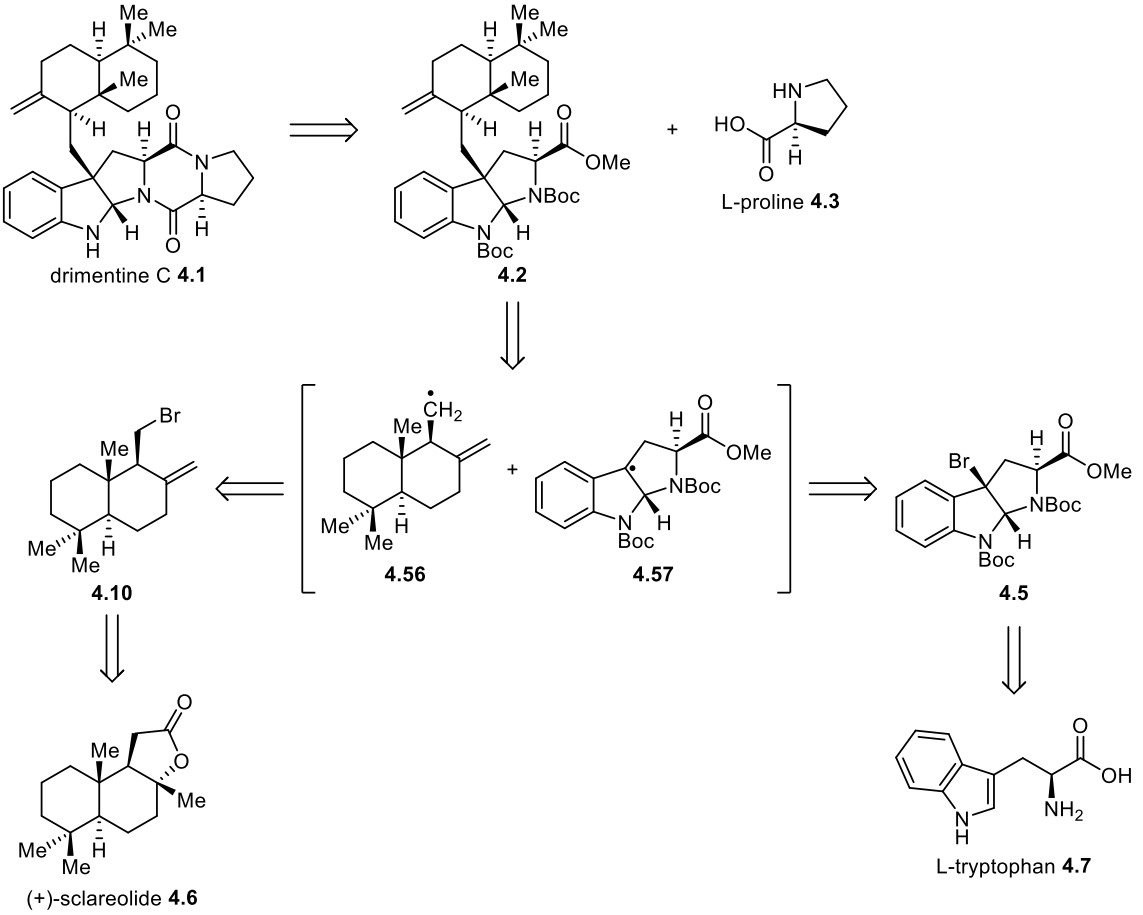
homodimerization and provided *exo*-**4.53** in 54% yield. Then, they epimerized **4.53** to the *endo*-diastereomer **4.54** by forming the enolate with lithium HMDS followed by kinetic protonation.




**Scheme 4.13** Use of cobalt-induced radical C3a-C3a′ dimerization in the total synthesis of (+)-WIN 64821

While we wanted to use radical-based chemistry to affect the key C–C bond forming event, we needed to bias the system toward selective heterocoupling of radicals **4.56** and **4.57**. We were intrigued by the possibility of using nickel-catalyzed reductive cross-coupling, where two electrophiles are cross-coupled using transition metal catalysis without the intermediacy of organometallic reagents. Importantly, the mechanism of reductive cross-coupling was proposed to utilize radical intermediates.[17–21] This would allow us to directly cross-couple bromides **4.10** and **4.5**, which can be quickly and easily

prepared from (+)-sclareolide (**4.6**) and L-tryptophan (**4.7**).

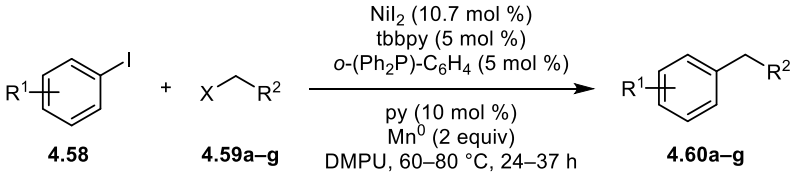



**Scheme 4.14** Second generation proposal for coupling to product 4.2

### 4.3.1 Background on Reductive Cross-Coupling

In nickel-catalyzed reductive cross-coupling, two alkyl halides undergo cross-coupling using nickel complexes in the presence of a reducing metal like $Zn^0$ or $Mn^0$.[19] This is conceptually similar to traditional Negishi cross-couplings[22] especially the "one-pot" cross-couplings;[23] however, no organometallic nucleophiles (e.g. organozincs) are formed *in situ* during reductive cross-coupling. While reductive cross-coupling with metals besides nickel (Co, Pd, Fe) are known,[19b] they will not be discussed.

Weix et al.[24] introduced reductive cross-coupling in a seminal paper in 2008 wherein they reported the reductive cross-coupling of aryl iodides with 1°-alkyl halides (X = I, Br) (Scheme 4.15). Using the dual-ligand catalyst system of $NiI_2$ (10.7 mol %) with tbbpy (5 mol %) and *o*-$(Ph_2P)_2$-$C_6H_4$ (5 mol %) and $Mn^0$ as the terminal reductant, iodobenzene **4.58** underwent cross-coupling with equimolar alkyl iodide **4.59a**, producing **4.60a** in 77% yield. Added pyridine (10 mol %) reduced β-hydride elimination. The reaction had high functional group tolerance (**4.60b–g**), providing cross-coupled products in good yields (65–85%). Alkyl bromides could be used as coupling partners (**4.60e–g**); however, the authors noted that selectivity for heterocoupling was greater if one of the coupling partners was an iodide. Nickel-catalyzed $sp^2$–$sp^3$ reductive cross-coupling has since been expanded to include aryl (including heteroaryl[25]) iodides, bromides, and chlorides;[26] 1°- and 2°-alkyl (including heterocyclic[25]) iodides, bromides,[27b] chlorides, and tosylates;[25b] allylic acetates;[27] and fluorinated alkyl bromides.[28] Recently, Reisman and coworkers[29] developed the first asymmetric reductive cross-coupling reactions between vinyl bromides and benzylic chlorides and between heteroaryl iodides and α-chloronitriles.

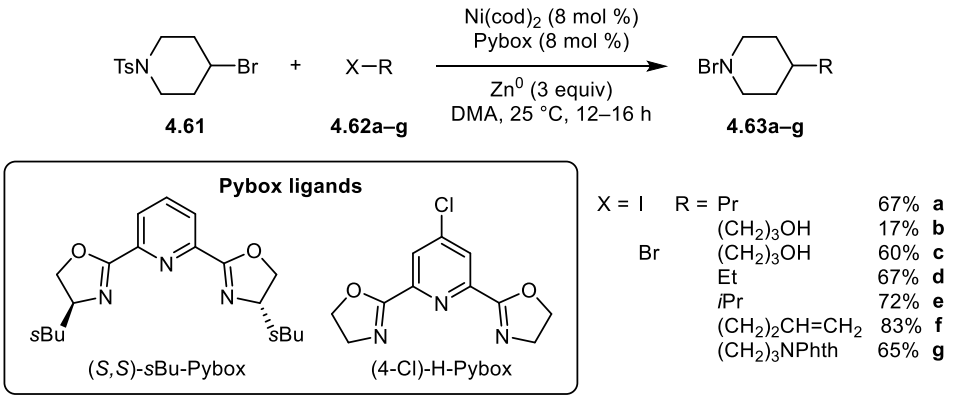



| | | | | | |
|---|---|---|---|---|---|
| X = I | $R^1$ = H | $R^2$ = | $(CH_2)_6CH_3$ | 77% | **a** |
| | OMe | | | 75% | **b** |
| | $CF_3$ | | | 75% | **c** |
| | C(O)H | | | 69% | **d** |
| X = Br | H | $R^2$ = | $(CH_2)_3CO_2Et$ | 77% | **e** |
| | | | $CH_2NHBoc$ | 85% | **f** |
| | | | $CH=C(CH_3)_2$ | 65% | **g** |

**Scheme 4.15** Nickel-catalyzed reductive cross-coupling of aryl iodides with alkyl halides

The first examples of nickel-catalyzed $sp^3$–$sp^3$ reductive coupling were homodimerizations.[30] In 2011, Gong et al.[31] published a seminal report on the nickel-

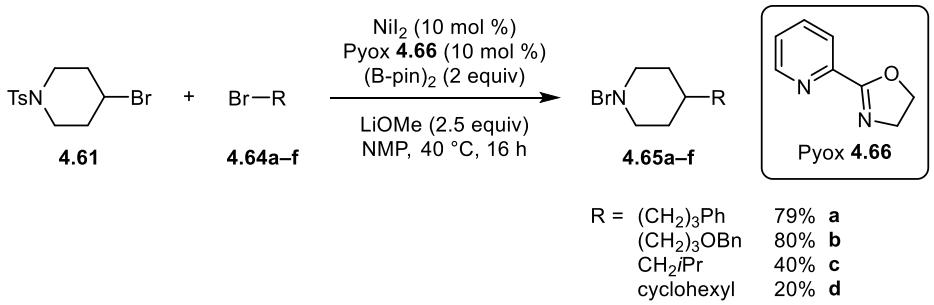
catalyzed reductive cross coupling of unactivated alkyl halides. 2°-Alkyl bromide **4.61** and excess 1°-alkyl halide (3 equiv) **4.62a** in the presence of $Ni(cod)_2$ (8 mol %), a Pybox (pyridine bisoxazoline) ligand (8 mol %), and $Zn^0$ (3 equiv) reacted to produce cross-coupled product **4.63a** in 67% yield (Scheme 4.16). (*S*,*S*)-*s*Bu-Pybox was optimal for alkyl bromides while (4-Cl)-H-Pybox was optimal for alkyl iodides. The yield of cross-coupled product was better when both coupling partners were alkyl bromides, which is in contrast to $sp^2$–$sp^3$ reductive cross-coupling. The reaction conditions were mild enough to accommodate unprotected alcohols (**4.63b–c**, 17 and 60%) and olefins (**4.63f**, 83%). A few 2°-alkyl–2°-alkyl cross-couplings were reported; these also went in good yield when both partners were bromides.




**Scheme 4.16** Nickel-catalyzed reductive cross-coupling of unactivated alkyl halides

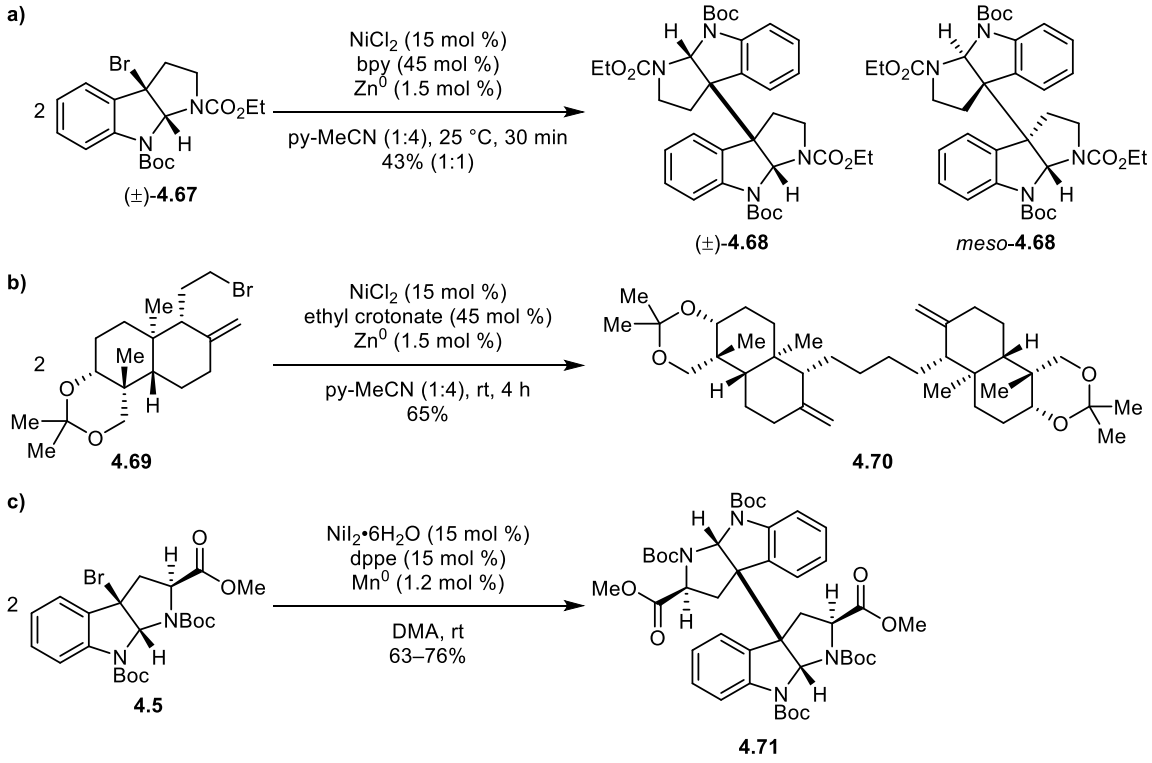
In 2013, Gong et al.[21] reported that the use of bis(pinacolato)diboron as the terminal reductant improved cross-coupling efficiency while minimizing competitive homocoupling. While outwardly similar to Suzuki cross-couplings using unactivated electrophiles,[32] preliminary mechanistic work indicated than an *in situ* organoborane/Suzuki process was unlikely. Bromide **4.61** underwent cross-coupling with a slight excess of bromide **4.64a** (1.5 equiv) using $NiI_2$ (10 mol %), Pyox **4.66** (10 mol %), $(B\text{-pin})_2$ (2 equiv), and lithium methoxide (2.5 equiv) in 1-methyl-2-pyrrolidinone (NMP) at 40 °C for 16 h to produce **4.65a** in 79% yield (Scheme 4.17). While simple 1°-

alkyl bromides and 2°-alkyl bromides containing polar functional groups underwent the reaction in good yield (**4.65b**, 80%), sterically-crowded 1°-alkyl bromides (**4.65c**, 40%) and 2°-alkyl bromides without polar functional groups (**4.65d**, 20%) were less efficient. The nickel-catalyzed $sp^3$–$sp^3$ reductive cross-coupling has since been expanded to intramolecular cross-couplings[33] and cross coupling of 2°-alkyl bromides with MeOTs.[34]




**Scheme 4.17** Nickel-catalyzed reductive cross-coupling of alkyl bromides using $(B\text{-pin})_2$ as the terminal reductant

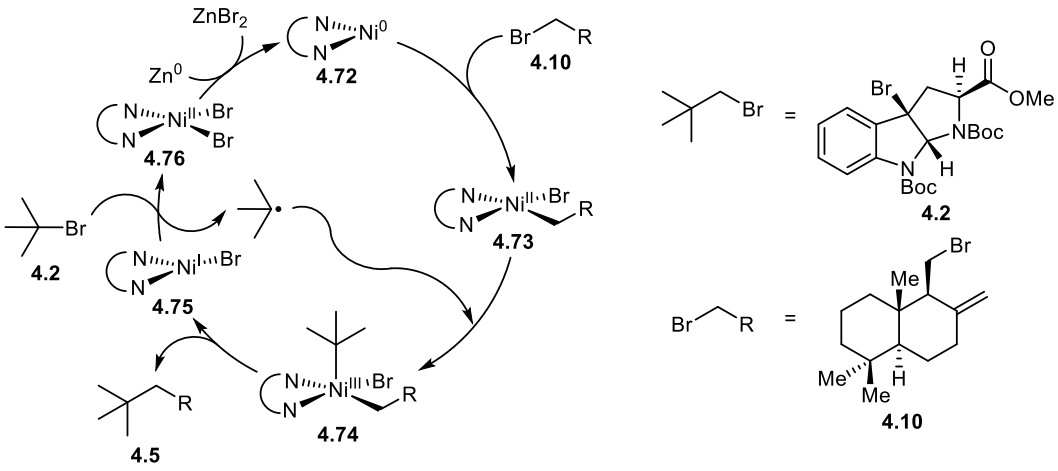
Thus far, all the examples have involved only 1°- or 2°-alkyl halides; reductive cross-coupling of 3°-alkyl halides is noticeably absent. Only within the past two years have there been reports of 3°-alkyl halides undergoing nickel-catalyzed reductive cross-coupling with alkyl acids[35] and aryl halides.[36] However, in 2013, Peng et al.[37] published the reductive homocoupling of bromopyrroloindolines. Upon treatment with $NiCl_2$ (15 mol %), bpy (45 mol %), and $Zn^0$ (1.5 mol %) in a mixture of pyridine and MeCN (1:4) at 25 °C, racemic bromopyrroloindoline **4.67** underwent homocoupling to produce a 1:1 mixture of (±)-**4.68** and *meso*-**4.68** in a combined 43% yield (Scheme 4.18a). Also of note, complex 1°-alkyl bromide **4.69** underwent homocoupling producing **4.70** in 65% yield (Scheme 4.18b); the exocyclic olefin was not affected. Additionally, *exo*-bromopyrroloindoline **4.5** underwent nickel-catalyzed reductive homodimerization under similar conditions to produce dimer **4.71** in 63–76% yield (Scheme 4.12c).[38] Epimerization of the C2-stereocenter was not observed.




**Scheme 4.18** Nickel-catalyzed reductive homodimerization: a) first example of 3°-alkyl bromide; b) sesquiterpenoid homocoupling; c) using bromopyrroloindoline **4.5**

We believed it would be possible to reductively cross-couple **4.5** and **4.10** using nickel-catalyzed reductive cross-coupling. Conditions would need to be chosen to minimize competitive homocoupling. This approach was attractive because the drimentine core would be accessed from the unactivated alkyl halides without the need to prepare an organometallic nucleophile from one of these precious substrates. Selectivity could be achieved by using an excess of one substrate (1.3–3.0 equiv). However, there should be some inherent selectivity for cross-coupling between the 1°-alkyl halide (I or Br) and the 3°-alkyl bromide due to the nature of the radical chain process proposed for nickel-catalyzed cross coupling wherein the 1°-alkyl halide undergoes normal, net-two-electron oxidative addition (1°-alkyl halides undergo oxidative addition faster than 3°-alkyl halides[39]) while the 3°-alkyl bromide serves as a radical precursor (3°-alkyl radicals are more stable than 1°-alkyl radicals).This was first proposed for reductive cross-

coupling of aryl halides and alkyl halides[40] but may be applicable to reductive cross-coupling between 3°-alkyl halides and 1°-alkyl halides (Scheme 4.19).



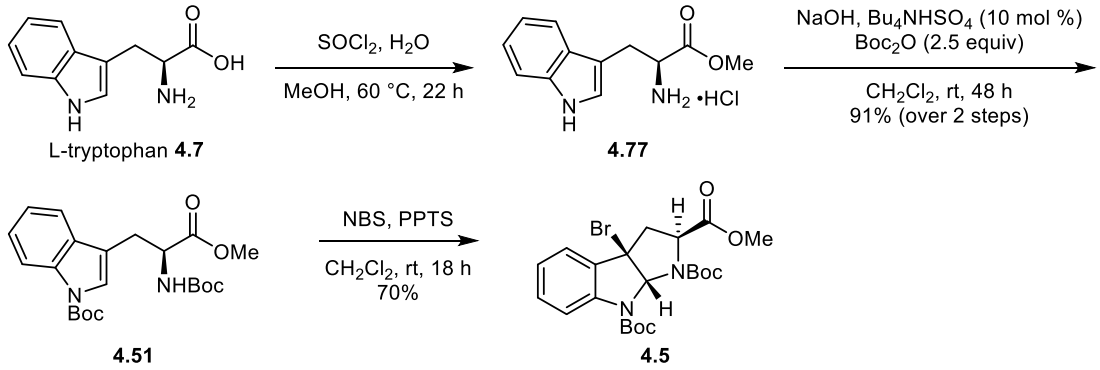

**Scheme 4.19** Plausible radical chain mechanism for nickel-catalyzed reductive cross-coupling of 1°-alkyl bromides with 3°-alkyl bromides

### 4.3.2 Synthesis of Alkyl Bromides 4.5 and 4.10

Bromopyrroloindoline **4.5** was prepared in three steps from L-tryptophan (**4.7**). Using the procedure from Makinen et al.[41] heating L-tryptophan (**4.7**) with thionyl chloride and water in methanol at 60 °C for 22 hours produced L-tryptophan methyl ester **4.77**, which was carried into the next reaction without purification (Scheme 4.20).

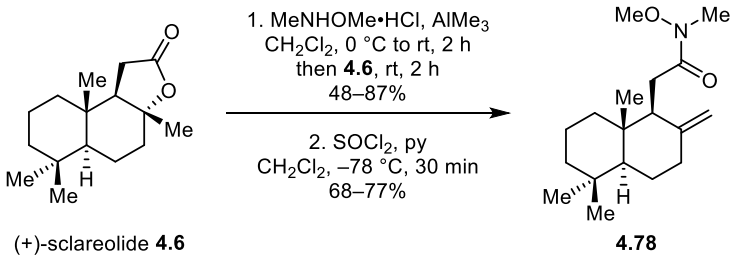
Boc protection of the two nitrogens was initially attempted by reacting **4.77** with $Boc_2O$ (2.5 equiv), sodium hydroxide, and phase-transfer catalyst $Bu_4NCl$ (10 mol %) in $CH_2Cl_2$ at room temperature for 18 hours. However, bis-protected **4.51** was obtained in only 18% yield; the majority of the recovered material (68%) had been mono-protected. If the reaction time was increased to 66 hours, **4.51** was obtained in 79% yield (over the two steps). Changing the phase-transfer catalyst to $Bu_4NHSO_4$, as reported by Danishefsky et al.,[9b] greatly increased the efficiency of the protection. **4.51** was obtained in 91% yield (over two steps) after allowing to react at room temperature for 48 hours.

The next step was bromocyclization of **4.51** to provide key bromopyrroloindoline **4.5**.[11] Protected L-tryptophan **4.51** was stirred with NBS and PPTS in $CH_2Cl_2$ for 18 hours at room temperature. After purification by column chromatography, *exo*-**4.5** was isolated in 74% yield.




**Scheme 4.20** Synthesis of bromopyrroloindoline **4.5**

Coupling partner **4.10** was synthesized from (+)-sclareolide (**4.6**) in four steps. Lactone ring-opening to the Weinreb amide with subsequent dehydration, previously discussed in Chapter 3, provided olefin **4.78** (Scheme 4.21).[42]

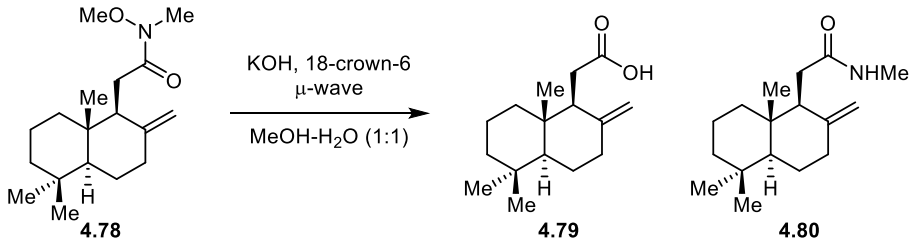



**Scheme 4.21** Lactone ring-opening of **4.6** to the Weinreb amide and dehydration

The next step was hydrolysis of **4.78** to carboxylic acid **4.79**. When **4.78** was allowed to react with potassium hydroxide (4 equiv) in a 1:1 mixture of methanol and water at 140 °C for 40 minutes in a microwave reactor, starting material was not fully

consumed, and carboxylic acid **4.79** was produced in a mixture with methyl amide **4.80** (Table 4.3, entry 1). During purification by column chromatography, Weinreb amide **4.78** and carboxylic acid **4.79** co-eluted, so yields were not obtained; methyl amide **4.80** was isolated in 19% yield. Increasing the reaction time slightly increased conversion (entry 2). The addition of 18-crown-6 (1 equiv) with further increase in the excess of potassium hydroxide (10 equiv) led to full conversion of **4.78** in 20 min; however, selectivity was poor, with **4.79** and **4.80** being produced in a 1:1 mixture (entry 3). Increasing the reaction time did not improve the selectivity; however, **4.79** could be isolated in 41% yield (entry 4).

**Table 4.3** Optimization of Weinreb amide **4.78** hydrolysis using a microwave reactor




**4.78** **4.79** **4.80**

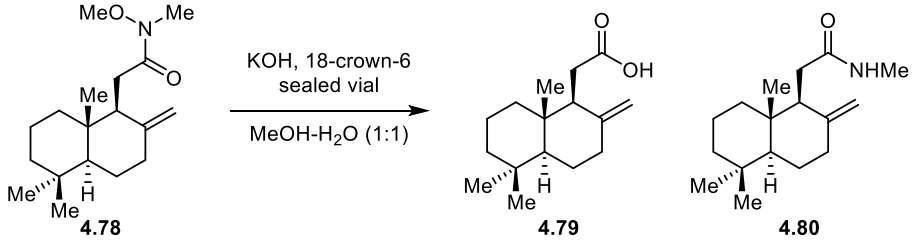
| Entry[a] | KOH (equiv) | 18-crown-6 (equiv) | Temp (°C) | Time (min) | **4.78** : **4.79** : **4.80** | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1[c] | 4.0 | - | 130–150 | 20 | 1 : 3 : 2 | -[d] |
| 2[c] | 4.0 | - | 140 | 40 | 1 : 7 : 5 | -[d] |
| 3 | 10.0 | 1.0 | 145–150 | 20 | 0 : 1 : 1 | -[d] |
| 4 | 10.0 | 1.0 | 145 | 40 | 0 : 1 : 1 | 41 |

[a] Reactions run on 0.1 g scale. [b] Isolated yield of carboxylic acid **4.79**. [c] Reaction run on 0.04 g scale. [d] Carboxylic acid **4.79** not isolated.

We hypothesized that methyl amide **4.80** could be an intermediate in the hydrolysis and that increasing the reaction time could push the hydrolysis to completion. Since the reaction would be longer than that typically recommended for a microwave reactor, it was instead heated in a sealed vial with a PTFE-lined cap using an aluminum

block heater. After heating **4.78** with potassium hydroxide (4 equiv) in MeOH-$H_2O$ (1:1) at 130 °C for 45 hours, carboxylic acid **4.79** was isolated in 70% yield (Table 4.4, entry 1). The $^1$H NMR spectrum showed a much improved product ratio of 5:1 (**4.79**:**4.80**). When the equivalency of potassium hydroxide was increased (10 equiv, entry 2), the reaction was less successful; although, this may have been due to cap failure. While the reaction suffered from poor solubility, the addition of ether solvent (1,4-dioxane, entry 3) resulted in no reaction. With the addition of 18-crown-6, both product ratios and yields became more reproducible, and the reaction went to full conversion (entries 4–6) within 25 h. Large increases in potassium hydroxide, 18-crown-6, and reaction time led to diminished selectivity for **4.79**, which made us revise our original hypothesis regarding methyl amide **4.80**. Instead, it seemed more likely that **4.80** was a decomposition byproduct. Ultimately, it was determined that the cap failure rate was too high (~50% under these conditions). When the cap failed and solvent evaporated, the selectivity of **4.79** decreased.

**Table 4.4** Optimization of Weinreb amide **4.78** hydrolysis using sealed vials




**4.78** **4.79** **4.80**

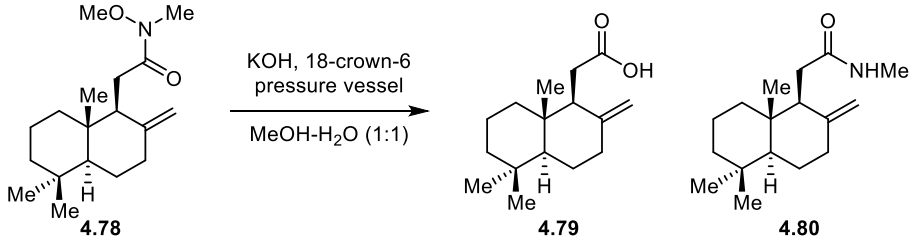
| Entry[a] | KOH (equiv) | 18-crown-6 (equiv) | Temp (°C) | Time (h) | **4.78** : **4.79** : **4.80** | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | 4.0 | - | 130 | 45 | 0 : 5 : 1 | 70[c] |
| 2[d] | 10.0 | - | 130 | 27 | 1 : 5 : 3 | 39 |
| 3[e,f] | 10.0 | - | 130 | 43 | 1 : 0 : 0 | - |
| 4 | 10.0 | 1.0 | 130 | 25 | 0 : 3 : 1 | 37 |
| 5[d] | 10.0 | 1.0 | 130 | 27 | 0 : 2 : 1 | 46[c] |
| 6 | 10.0 | 1.0 | 130 | 27 | 0 : 5 : 1 | 53[g] |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | 20.0 | 3.0 | 130–140 | 96 | 0 : 1 : 3 | 52 |

[a] Reactions run on 0.1 g scale. [b] Isolated yield of carboxylic acid **4.79**. [c] Given as an average of two runs. [d] PTFE-lined cap failed during reaction. [e] Reaction run on 0.3 g scale. [f] Used 1,4-dioxane instead of MeOH. [g] Given as an average of three runs.

To make the hydrolysis more reliable, the reaction was conducted in a sealed pressure vessel that was heated in an oil bath. In addition to improvement in reaction selectivity and isolated yield, the hydrolysis reactions could now be run on larger scale.

**Table 4.5** Optimization of Weinreb amide **4.78** hydrolysis using sealed pressure vessel




**4.78** **4.79** **4.80**

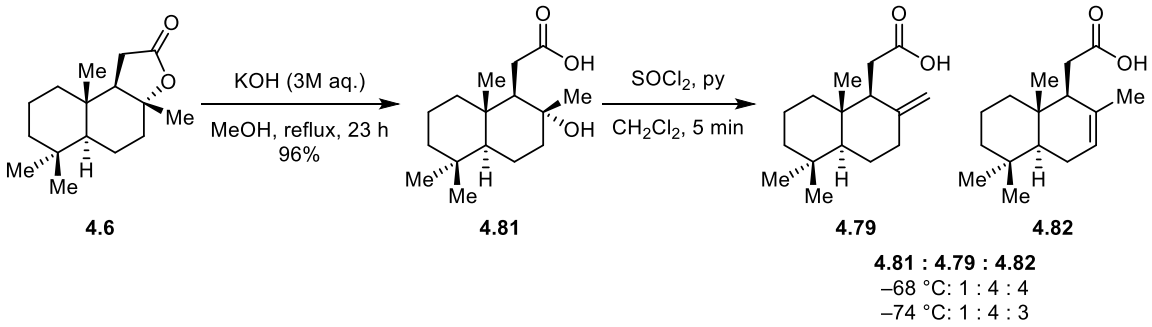
| Entry | KOH (equiv) | 18-crown-6 (equiv) | Temp (°C) | Time (h) | **4.78** : **4.79** : **4.80** | Yield (%)[a] |
|---|---|---|---|---|---|---|
| 1 | 10.0 | 1.0 | 130 | 27 | 0 : 4 : 1 | 67 |
| 2 | 10.0 | 1.0 | 130 | 55 | 0 : 7 : 1 | 50 |

[a] Isolated yield of carboxylic acid **4.79**.

At this point, we discovered that (+)-sclareolide (**4.6**) could be opened to carboxylic acid **4.79** directly,[43] which shortened the synthesis of bromide **4.5** by one step. Heating of **4.6** with aqueous potassium hydroxide in methanol at reflux for 23 hours provided crude carboxylic acid **4.81** in 96% average yield (Scheme 4.22). While we had initially been concerned about relactonization, **4.81** was stable at room temperature in air for up to 3 months.

Unfortunately, dehydration to the exocyclic olefin **4.79** was less selective than for the corresponding Weinreb amide. However, a lower temperature (–74 °C) for a shorter

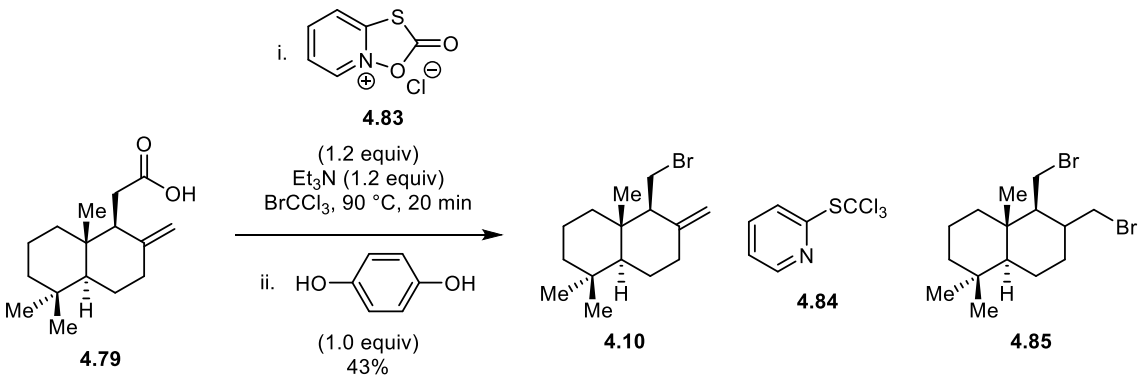
reaction time (5 minutes) improved selectivity between **4.79** and **4.82**. The reactions were stopped within 5 minutes after completion of the addition of the thionyl chloride/pyridine solution (over 15 minutes) by quenching with saturated sodium bicarbonate in methanol. Purification by column chromatography was challenging; from the reaction at –74 °C, **4.79** was isolated in 15% yield. Because of the challenge of forming the exocyclic olefin selectively in the presence of the carboxylic acid, the initial route via Weinreb amide **4.78** and hydrolysis using a pressure vessel is ultimately preferable.




**Scheme 4.22** Lactone-ring opening to **4.81** and subsequent dehydration

Key bromide **4.10** was prepared via a Barton decarboxylative bromination (Scheme 4.23). An attempt to initiate this radical reaction with visible light[44] (300 W) was unsuccessful; after 2 hours, only starting material was recovered. In their original work, Barton and coworkers[45] initiated decarboxylative bromination thermally. So, decarboxylative bromination of **4.79** was pursued using thermal initiation. Carboxylic acid **4.79**, Barton salt **4.83**, and triethylamine were refluxed in bromotrichloromethane for 3.5 hours, whereupon the crude reaction mixture was analyzed by GCMS (low resolution CI mass spectrometry). Bromide **4.10** along with byproducts **4.84** and **4.85** were identified and confirmed by $^{1}$H NMR spectroscopy. However, isolation of **4.10** was unsuccessful. We hypothesized that this was due to the continued presence of radicals in the crude product mixture. When the reaction mixture was quenched with hydroquinone followed by an acidic workup, byproduct **4.85** was no longer present. However, yields of

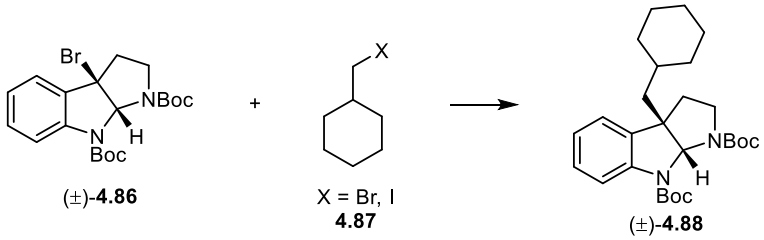
bromide **4.10** were still low, so the reaction time and temperature were reduced. Ultimately, heating **4.79** with Barton salt **4.83** and triethylamine in bromotrichloromethane at 90 °C for 20 minutes yielded bromide **4.10** in 43% after column chromatography.




**Scheme 4.23** Barton decarboxylative bromination of carboxylic acid **4.79**

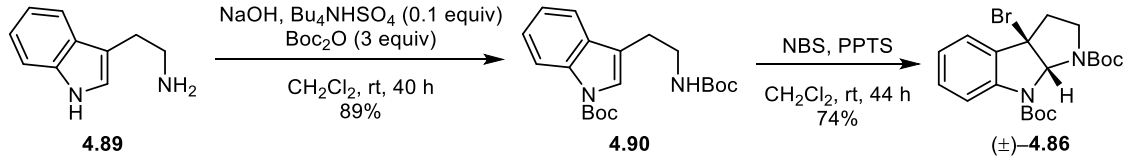
### 4.3.3 Reductive Cross-Coupling Model Studies

In order to test the feasibility of the proposed nickel-catalyzed reductive cross-coupling (especially because, at that time, the reductive cross-coupling of 3°-alkyl halides was unprecedented), we decided to attempt it first on model substrates (±)-**4.86** and **4.87**, which would result in (±)-**4.88** (Scheme 4.24).




**Scheme 4.24** Model substrates for nickel-catalyzed reductive cross-coupling

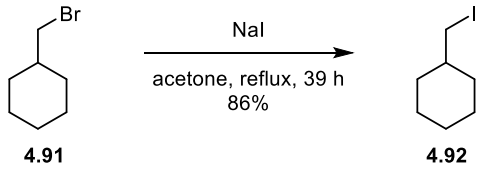
Racemic bromopyrroloindoline **4.86** was prepared analogously to bromopyrroloindoline **4.5** (Scheme 4.25).[9b,11] Reacting tryptamine **4.89** with $Boc_2O$ (3 equiv), sodium hydroxide, and $Bu_4NHSO_4$ (0.1 equiv) in $CH_2Cl_2$ at room temperature for 40 hours provided protected tryptamine **4.90** in 89% average yield. Bromocyclization of **4.90** (74% average yield) was accomplished by reacting with NBS and PPTS in $CH_2Cl_2$ at room temperature for 44 hours.




**4.89** **4.90** (±)–**4.86**

**Scheme 4.25** Synthesis of model bromopyrroloindoline **4.86**

(Bromomethyl)cyclohexane **4.91** and (iodomethyl)cyclohexane **4.92** were chosen as models for bromide **4.10**. (Bromomethyl)cyclohexane **4.91** has the benefit of being commercially-available. (Iodomethyl)cyclohexane **4.92** was prepared by a Finkelstein reaction of **4.91** (Scheme 4.26).[46] Refluxing (bromomethyl)cyclohexane **4.91** with sodium iodide in acetone for 39 hours provided crude **4.92** in 86% yield.




**4.91** **4.92**

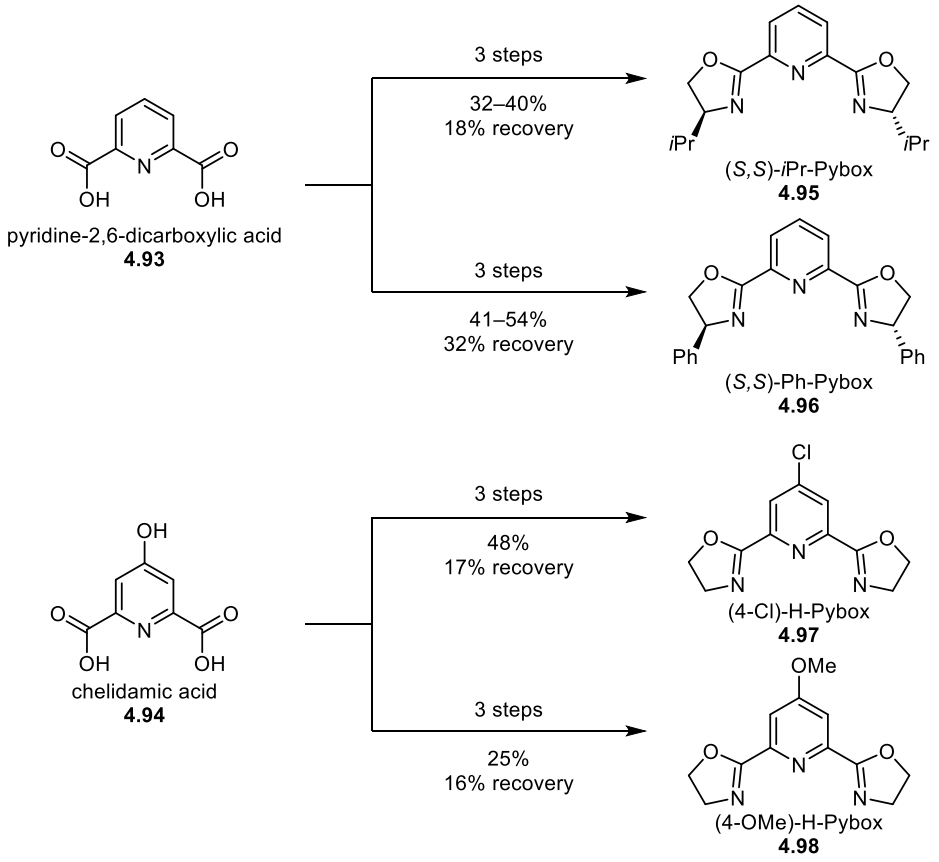
**Scheme 4.26** Finkelstein reaction of (bromomethyl)cyclohexane **4.91**

In order to conduct a successful cross-coupling between alkyl halides, competitive β-hydride elimination must be minimized. The ligand has been shown to play a key role in this.[47] Additionally, the optimal ligand is highly substrate dependent, so it was of interest to have a variety of ligands to test in the reaction conditions. Pybox-based ligands been highly successful for nickel-catalyzed Negishi cross-couplings of unactivated alkyl

halides[48,49] as well as for the reductive cross-coupling of unactivated alkyl halides.[31] The chelating nature of pybox ligands was proposed to make β-hydride elimination unfavorable due to coordinate saturation.[48a] Other effective ligands include terpyridine (terpy),[49–50] Pincer,[51] and 2,2′-bipyridine (bpy).[24] We chose to screen four Pybox ligands ((*S*,*S*)-*i*Pr-Pybox, (*S*,*S*)-Ph-Pybox, (4-Cl)-H-Pybox, and (4-OMe)-H-Pybox) along with three bpy ligands (bpy, 4,4′-*t*Bu-2,2′-bipyridyl (tbppy), and bathophenanthroline (BPhen)).

Pybox ligands were synthesized in three steps each according to literature procedures (Scheme 4.27),[31,52] from pyridine-2,6-carboxylic acid (**4.93**) and chelidamic acid (**4.94**). (*S*,*S*)-*i*Pr-Pybox (**4.95**) was synthesized in 32–40% yield with 18% recovery after recrystallization. (*S*,*S*)-Ph-Pybox (**4.96**) was synthesized in 41–54% yield with 32% recovery after recrystallization. (4-Cl)-H-Pybox (**4.97**) was synthesized in 48% yield with 17% recovery after recrystallization. (4-OMe)-H-Pybox (**4.98**) was synthesized in 25% yield with 16% recovery after recrystallization. The bpy ligands were commercially available.‡‡

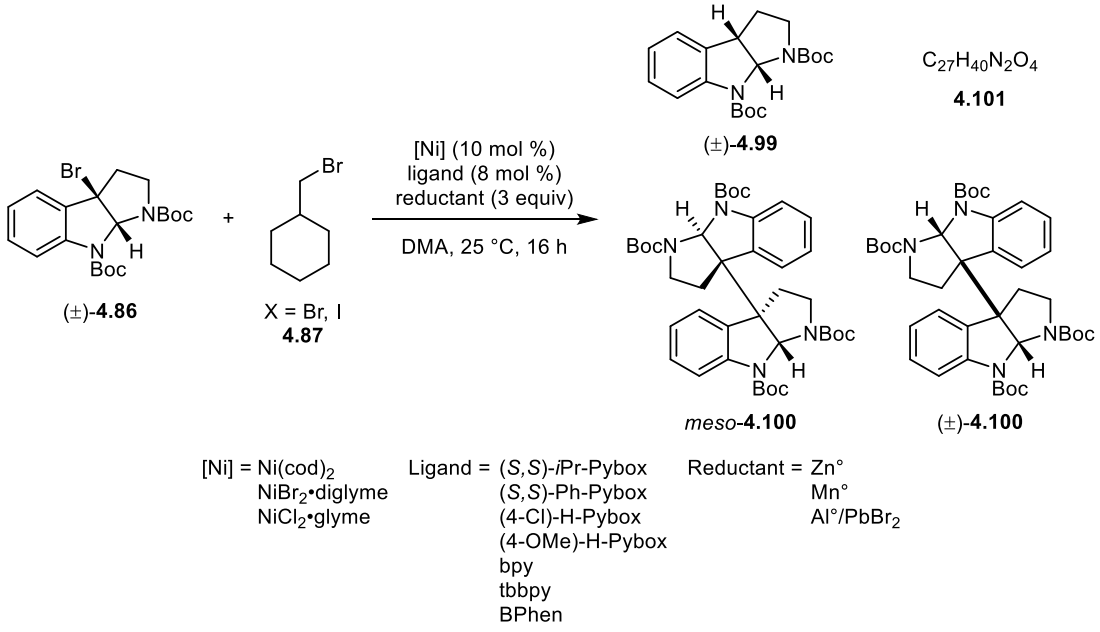
‡‡ Tbbpy was synthesized by Dr. Kathryn A. McGarry following the literature procedure: Awad, D. J.; Schilde, U.; Strauch, P. *Inorg. Chim. Acta* **2011**, *365*, 127–132.



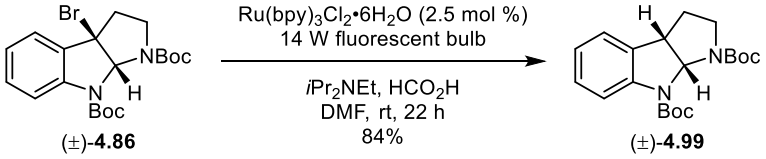

**Scheme 4.27** Synthesis of Pybox ligands

Bromides (±)-**4.86** and **4.87** were reacted with $Ni(cod)_2$ or $NiBr_2$•diglyme (10 mol %), ligand (8 mol %), and $Zn^0$ (3 equiv) in DMA at 25 °C using an aluminum block heater for 16 hours (Scheme 4.28). The reactions were conducted in 1-dram vials with PTFE-lined caps and were set up on the benchtop. The crude reaction mixtures were analyzed by LC-ESIMS. The reaction mixtures had LC traces with four peaks each. The first peak had a mass corresponding to the chemical formula $[2(C_{20}H_{28}N_2O_4) + Na]^+$ (*m/z* 743.6), which was determined to be the byproduct resulting from reduction of bromopyrroloindoline **4.86**. This was confirmed by independent synthesis of (±)-**4.99** (Scheme 4.29). Following the procedure of Stephenson et al.,[53] bromopyrroloindoline **4.86** was reacted with Hunig's base and formic acid in DMF at room temperature under photoredox conditions: $Ru(bpy)_3Cl_2$•$6H_2O$ (2.5 mol %) and irradiation with a 14 W

fluorescent bulb. Pyrroloindoline (±)-**4.99** was isolated in 84% yield.



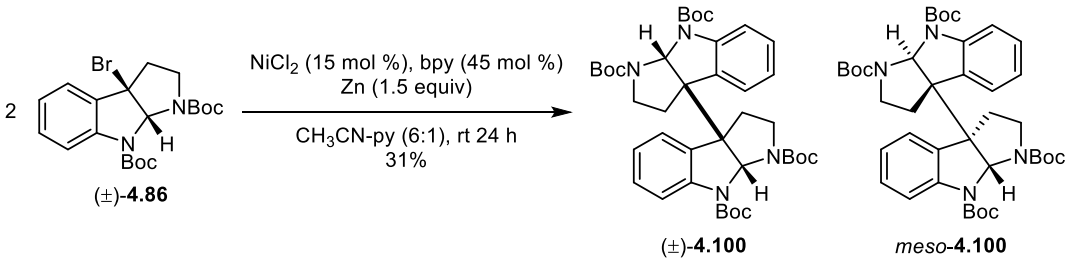

**Scheme 4.28** Nickel-catalyzed reductive cross-coupling model studies




**Scheme 4.29** Independent synthesis of reduction byproduct (±)-**4.99**

The second and third peaks in the LC traces both had masses which corresponded to $[C_{40}H_{54}N_4O_8 + Na]^+$ (*m/z* 741.6). These were determined to be the (±)- and *meso*-homodimers **4.100**. Again, their identities were confirmed by independent synthesis (Scheme 4.30). Following the procedure of Peng et al.,[37] bromopyrroloindoline (±)-**4.86** was subjected to nickel-catalyzed reductive homocoupling using $NiCl_2$•glyme (15 mol %), bpy (45 mol %), and $Zn^0$ (1.5 equiv) in a 6:1 MeCN/pyridine mixture at room temperature for 24 hours. The active catalyst was prepared by pre-mixing $NiCl_2$•glyme, bpy, and $Zn^0$ in MeCN/pyridine and heating at 55 °C for 10 minutes prior to cooling to

room temperature and adding **4.86**. The mixture of dimer diastereomers was isolated in 31% yield.




**Scheme 4.30** Independent synthesis of (±)- and meso-homodimers **4.100**

The fourth peak (**4.101**) had a *m/z* of 479.3, which corresponded to a chemical formula of $[C_{27}H_{40}N_2O_4 + Na]^+$. This chemical formula would correspond to the desired cross-coupled product (±)-**4.88**. However, chemical formulas do not denote connectivity. It could also correspond to (±)-**4.102** where the cross-coupling occurred at the aromatic ring with concomitant reduction of the pyrroloindoline. If this occurred, the alkyl group would likely be attached to C5, since pyrroloindolines are known to react similar to anilines.[3]

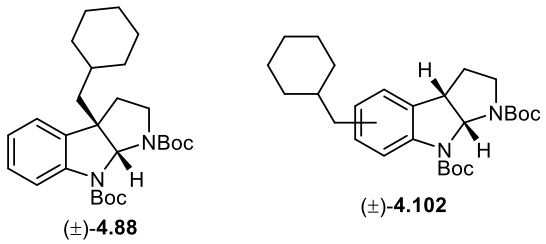
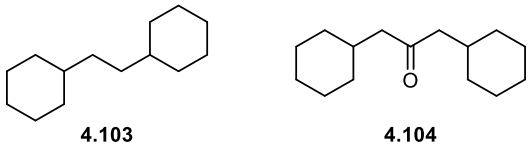



**Figure 4.1** Potential structures of unknown **4.101**

At this point, the goal was to conclusively determine the structure of unknown product **4.101**. Other nickel sources ($NiCl_2$•glyme), reductants ($Mn^0$ and $Al^0/PbBr_2$), and solvents (DMF and DMPU) were tested to see if selectivity for unknown **4.101** could be improved (Scheme 4.28). $Al^0/PbBr_2$ was tested as a reductant because it was known that

it serves as an electron pool.[54] Ultimately, the selectivity remained about the same for all reaction conditions tested. $Ni(cod)_2$ (10 mol %), tbbpy (8 mol %), and $Zn^0$ (3 equiv) were chosen as the catalyst conditions for scale-up in part because they provided the qualitatively "cleanest" reaction as well as all being commercially-available. Using these conditions 1.8 g of **4.86** was reacted with **4.87** in DMA at 25 °C for 16 hours. Column chromatography (15% EtOAc/hexanes) allowed for isolation of **4.99** and **4.100** as mixtures. The third fraction contained **4.99** and (±)-**4.100**; the fourth fraction contained (±)-**4.100** and *meso*-**4.100**. A second column (10% EtOAc/pentane) of the first fraction from the initial column allowed for the isolation of homodimer **4.103** and ketone **4.104**.

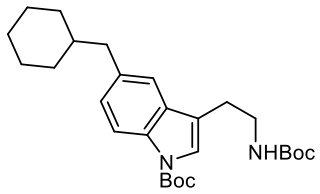



4.103 4.104

**Figure 4.2** Additional byproducts of the nickel-catalyzed reductive cross-coupling reactions

Subjection of the second fraction from the initial column to a second round of column chromatography (20% EtOAc/pentane) allowed for the isolation of unknown **4.101** as a mixture with **4.99**. Finally, subjection of this fraction to column chromatography (5% $Et_2O/CH_2Cl_2$) using MPLC-grade silica gel allowed for isolation of ~3 mg of pure **4.101**. This was subjected to a battery of NMR spectroscopic experiments: $^1H$, COSY, HSQC, HMBC, and HSQC-TOCSY. By $^1H$ NMR, both Boc groups were still present and there were four protons in the aromatic region. A broad peak at 4.5 ppm had no cross-peaks in the HSQC, which meant that it was attached to a nitrogen, in disagreement with either proposed structure **4.88** or **4.102** (Figure 4.1). In the HMBC, the peak at 2.5 ppm, which corresponded to the methylene of the (methyl)cyclohexyl group, had cross-peaks with three carbons in the aromatic region. Ultimately, the position of the (methyl)cyclohexylgroup was determined by chemical shifts and coupling constant analysis of the aromatic protons. Its structure is given in Figure 4.3; cross-coupling had

occurred at C5, and the pyrrolindoline had opened back to tryptamine. This was completely unexpected; furthermore, it was also not the desired cross-coupling. Therefore, we moved from this strategy to the third generation proposed synthesis of drimentine C (**4.1**) by a convergent route.

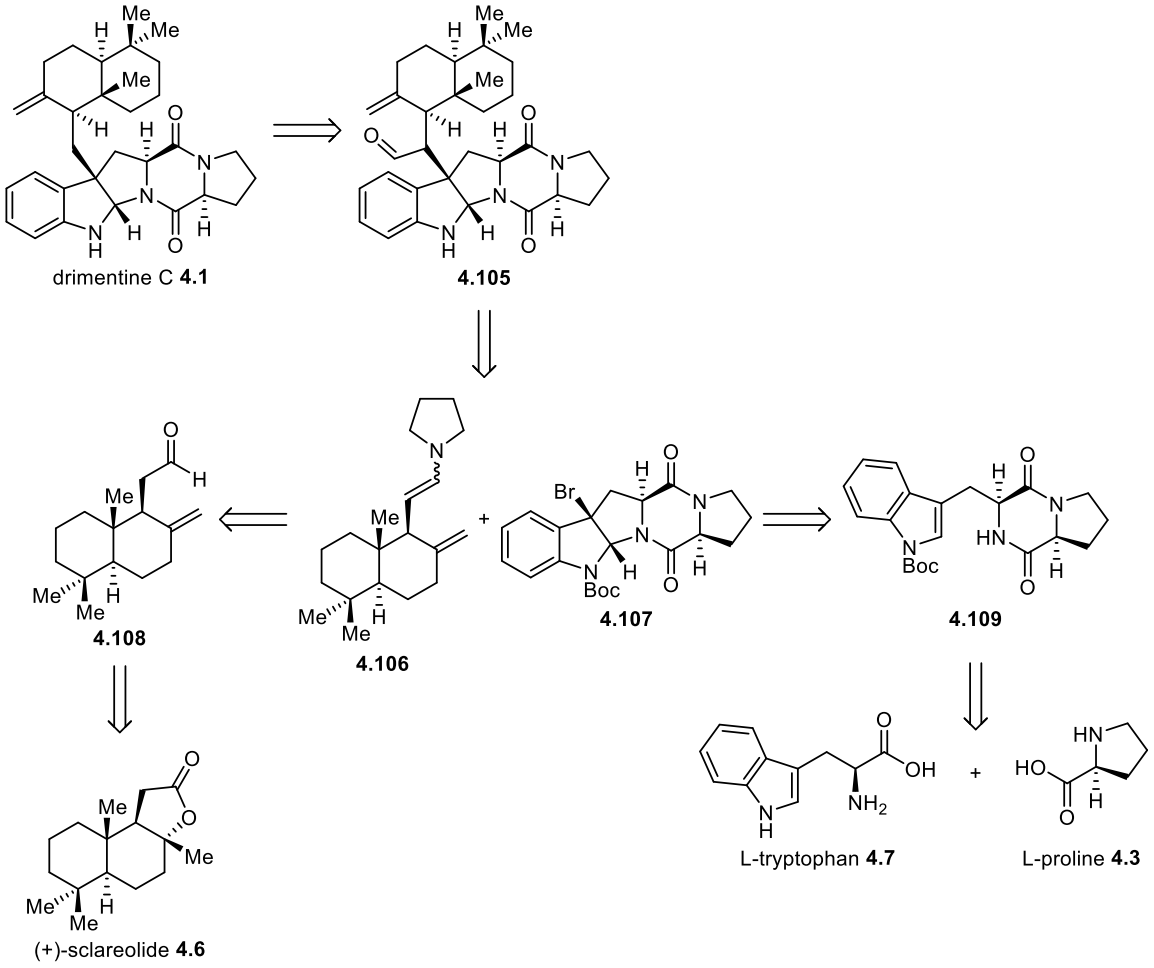



**4.101**

**Figure 4.3** Identity of unknown **4.101**

## 4.4 Third Generation Synthetic Route to Drimentine C

Our next strategy involved photoredox catalysis. This approach was attractive to us because its mode of activation involves single-electron transfer (SET) and, therefore, should not affect the C2 stereocenter. Like the previous routes, it builds complexity quickly from chiral starting materials: L-proline (**4.3**), (+)-sclareolide (**4.6**), and L-tryptophan (**4.7**). Here, a key difference is the ordering of events. We chose to have the diketopiperazine in place prior to carrying out the bond-formation between the pyrroloindoline and sesquiterpene fragments. Drimentine C (**4.1**) would be prepared from deprotection and deformylation of **4.105** (Scheme 4.31). The key step is an α-alkylation of enamine **4.106** with bromopyrroloindoline **4.107** using photoredox catalysis. Enamine **4.106** can be prepared from aldehyde **4.108**, which is three steps from (+)-sclareolide (**4.7**). Bromocyclization of **4.109** would provide bromopyrroloindoline **4.107**. Dipeptide **4.109** could be obtained from complementarily-protected derivatives of L-proline (**4.3**) and L-tryptophan (**4.7**).




**Scheme 4.31** Third generation proposal for the convergent synthesis of drimentine C

### 4.4.1 Background on Photoredox Catalysis

In photoredox catalysis, the excitation of a metal complex by visible light opens up the manifold of SET processes to organic molecules.[55] The process begins with the absorption of a photon by the photocatalyst to generate a high energy excited state. Typical photocatalysts are bench-stable polypyridyl complexes of ruthenium or iridium (Figure 4.4), which absorb high-energy visible light (400–475 nm). Use of visible light minimizes undesired reactivity from the direct excitation of the organic substrates as typical organic molecules require ultraviolet light for excitation. Organic dyes (Eosin Y and Rose Bengal) have also been used as photocatalysts; however, their absorbance is

red-shifted (539 nm for Eosin Y), so they have less energy when in an excited state to apply to the promotion of reactions.

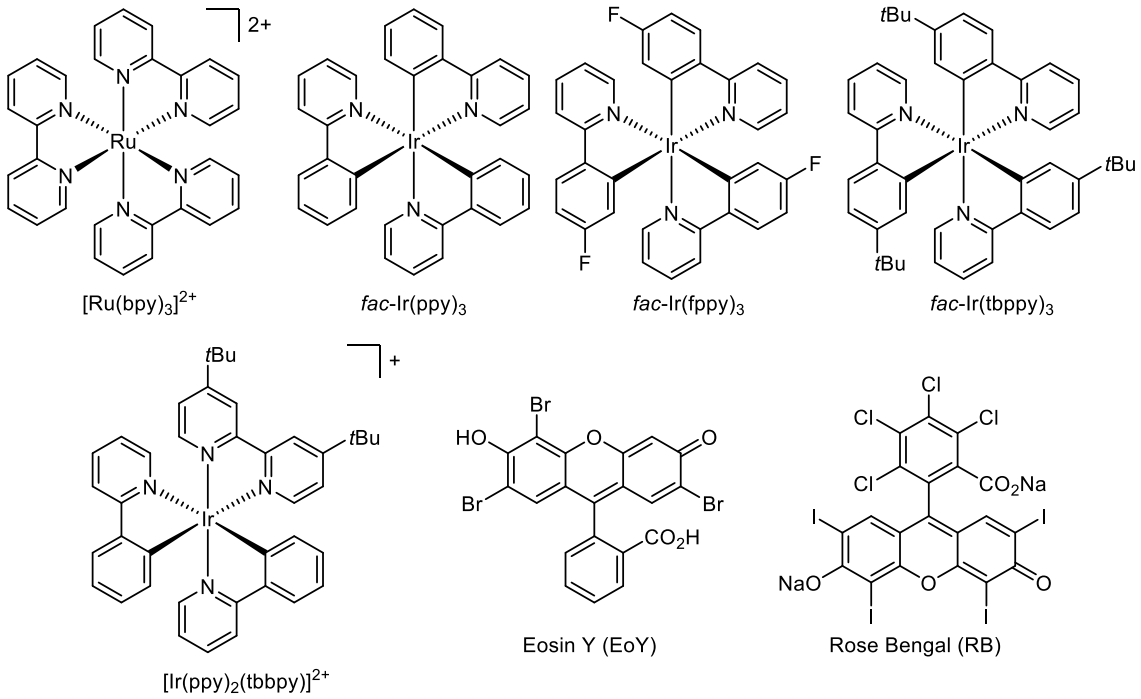



**Figure 4.4** Example photoredox catalysts

The ruthenium and iridium complexes are described by oxidations at the metal center and reductions at the ligands, termed metal-to-ligand charge transfer (MLCT). After excitation, the photocatalyst (*P) relaxes first to the lowest spin-allowed singlet excited state [*P $^{1}MLCT_{1}$]. This rapidly undergoes intersystem crossing and internal conversion to the long-lived first triplet excited state [*P $^{3}MLCT_{1}$], which has a sufficiently long lifetime ($Ru(bpy)_3Cl_2$: $\tau$ = 1100 ns) to undergo bimolecular quenching reactions. By changing the electronics of the ligands, the redox reactivity of the photocatalyst can be tuned. Electron donation from the ligand makes oxidation of the metal more facile, while electron-rich ligands lead to more negative reduction potential. The reactivity of photoredox catalysts can be approximated based on the reduction potentials of the ground state and of the excited state (Table 4.6).

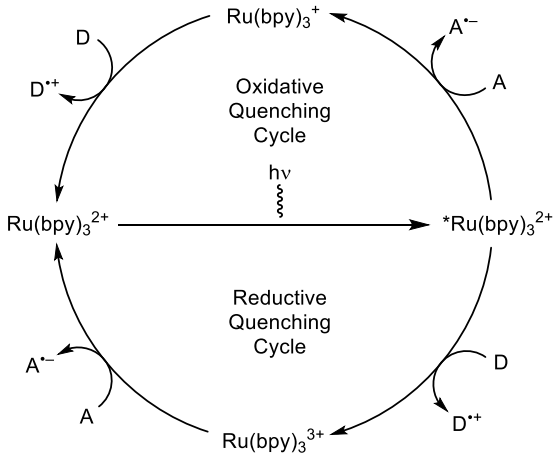
**Table 4.6** Redox potentials of commonly utilized visible light photocatalysts

| Entry | Photocatalyst | $E_{1/2}$ $(M^+/M)^a$ | $E_{1/2}$ $(M/M^-)^a$ | $E_{1/2}$ $(M^+/M^*)^a$ | $E_{1/2}$ $(M^*/M^-)^a$ | Ref. |
|---|---|---|---|---|---|---|
| 1 | Rose Bengal | +1.09 | –0.78 | –0.68 | +1.09 | 56 |
| 2 | $[Ru(bpy)_3]^{2+}$ | +1.29 | –1.33 | –0.81 | +0.77 | 57 |
| 3 | $[Ir(ppy)_2(tbbpy)]^+$ | +1.21 | –1.51 | –0.96 | +0.66 | 58 |
| 4 | Eosin Y | +0.72 | –1.14 | –1.60 | +1.18 | 58c |
| 5[b] | *fac*-$Ir(fppy)_3$ | +1.05 | –2.09 | –1.82 | +0.78 | 59 |
| 6[b] | *fac*-$(tbppy)_3$ | +0.74 | –2.23 | –1.86 | +0.37 | 59 |
| 7[b] | *fac*-$Ir(ppy)_3$ | +0.83 | –2.16 | –1.93 | +0.60 | 59 |

[a] All potentials are given in volts versus the saturated calomel electrode (SCE). Measurements were performed in MeCN at room temperature unless otherwise noted. [b] Converted from volts versus $Ag/AgCl_2$.

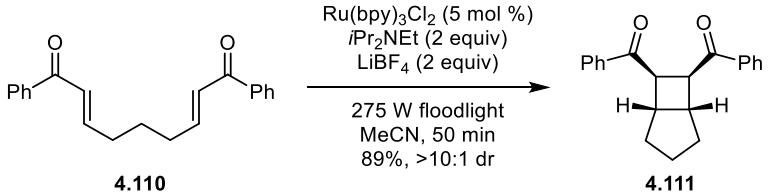
A key feature of photocatalysts is that they are poor single-electron oxidants and reductants in the ground state; however, their excited states are potent single-electron-transfer agents. Excitation of the photocatalyst generates a high energy electron and a lower energy hole. As such, the excited photocatalyst can act as either an oxidant (reductive quenching cycle) or reductant (oxidative quenching cycle). In the reductive quenching cycle, the excited photocatalyst, exemplified by $*Ru(bpy)_3^{2+}$ (Scheme 4.32), accepts an electron from a donor (D) to generate $Ru(bpy)_3^+$ and a radical cation ($D^{\bullet+}$). $Ru(bpy)_3^+$ then donates an electron to an acceptor (A), which regenerates a radical anion ($A^{\bullet-}$) ground state $Ru(bpy)_3^{2+}$. Tertiary amines are common donors in the reductive quenching cycle.

In the oxidative quenching cycle, $*Ru(bpy)_3^{2+}$ transfers a single electron to an acceptor (A). This generates a radical anion ($A^{\bullet-}$) and $Ru(bpy)_3^{3+}$, which is a strong oxidant. It accepts an electron from a donor (D) to produce a radical cation ($D^{\bullet+}$) and regenerate ground state $Ru(bpy)_3^{2+}$.




**Scheme 4.32** Oxidative and Reductive Quenching Cycles of $Ru(bpy)_3^{2+}$

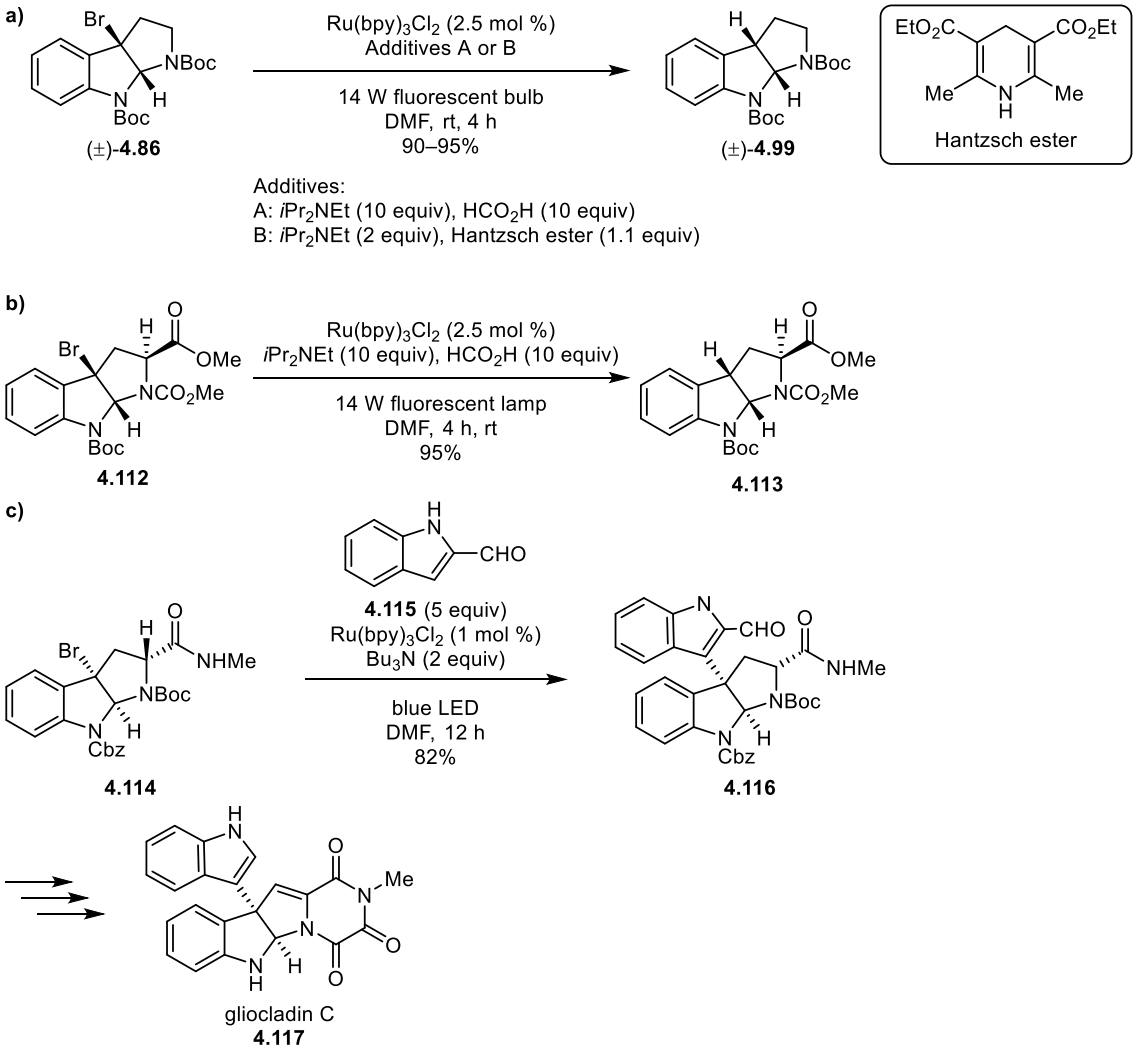
Between 2008 and 2009, three seminal reports[53,60–61] appeared, initiating great interest in the chemical community on utilizing photoredox catalysis to construct small molecules.[55] The first report, from Yoon et al.,[60] was a photocatalyzed [2+2] cycloaddition of bis(enones). Bis(enone) **4.110** (Scheme 4.33) underwent efficient cyclization to **4.111** (89%) upon visible light irradiation using $Ru(bpy)_3Cl_2$ (5 mol %) with added $LiBF_4$ (2 equiv) and Hunig's base (2 equiv). Bisketone **4.111** was obtained as the *meso*-diastereomer in excellent stereoselectivity (>10:1). Visible light, photocatalyst, and Hunig's base were all necessary for reactivity. $LiBF_4$ both increased the solubility of the $Ru(bpy)_3Cl_2$ in MeCN and acted as a Lewis acid; other counterions gave no reactivity.




**4.110** **4.111**

**Scheme 4.33** Photocatalytic [2+2] Cycloaddition of Bis(enones)

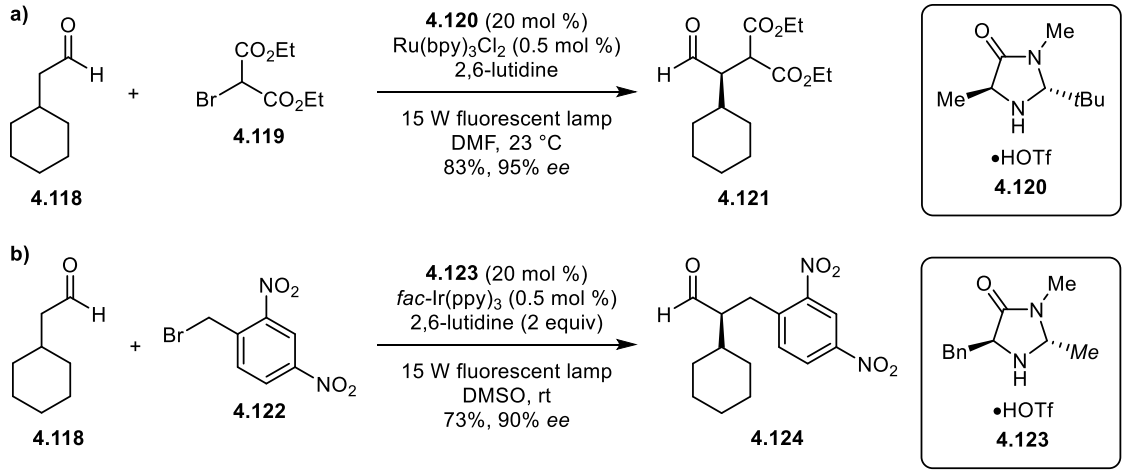
In 2009, Stephenson et al.[53] disclosed a photoredox-catalyzed reductive dehalogenation of activated alkyl halides. Bromopyrroloindoline (±)-**4.86** was subjected to irradiation by a 14 W fluorescent lamp with $Ru(bpy)_3Cl_2$ (2.5 mol %) in the presence of Hunig's base (10 equiv) and formic acid (10 equiv) in DMF for 4 hours producing pyrroloindoline (±)-**4.99** in 90% yield (Scheme 4.28a). We used this methodology in the independent synthesis (±)-**4.99** (see section 4.3.3). Alternatively, this reaction could be conducted with Hunig's base (2 equiv) and Hantzsch ester (1.1 equiv) providing (±)-**4.99** in 95% yield. Bromopyrroloindoline **4.112** also underwent the reaction in 95% yield using Hunig's base (10 equiv) and formic acid (10 equiv) as additives (Scheme 4.34b). They determined that Hunig's base was the primary hydrogen source in the reaction. Stephenson et al.[62] were able to trap the pyrroloindoline radical with indole, a key intermediate in their synthesis of gliocladin C.




**Scheme 4.34** Photoredox-catalyzed reductive dehalogenation reaction: a) using bromopyrroloindoline (±)-4.86; b) using bromopyrroloindoline 4.112; c) trapping with indole 4.115

MacMillan et al.[61] reported the first example of photoredox organocatalysis: a direct asymmetric α-alkylation of aldehydes (Scheme 4.35a). They combined photoredox catalysis with enamine catalysis. $Ru(bpy)_3Cl_2$ was excited with visible light then underwent a reductive quenching cycle. Sacrificial amine or enamine first reduced $*Ru(bpy)_3^{2+}$ to $Ru(bpy)_3^{+}$, which reduced electron-deficient bromide **4.119** to bromide and the corresponding radical. Meanwhile, aldehyde **4.118** formed an enamine with

imidazolidinone **4.120**. Combination of the organic radical with the enamine produced an α-alkylated amino radical, which served to further reduce $*Ru(bpy)_3^{2+}$ and continue the cycle. Upon hydrolysis, **4.121** was generated, and **4.120** was regenerated.



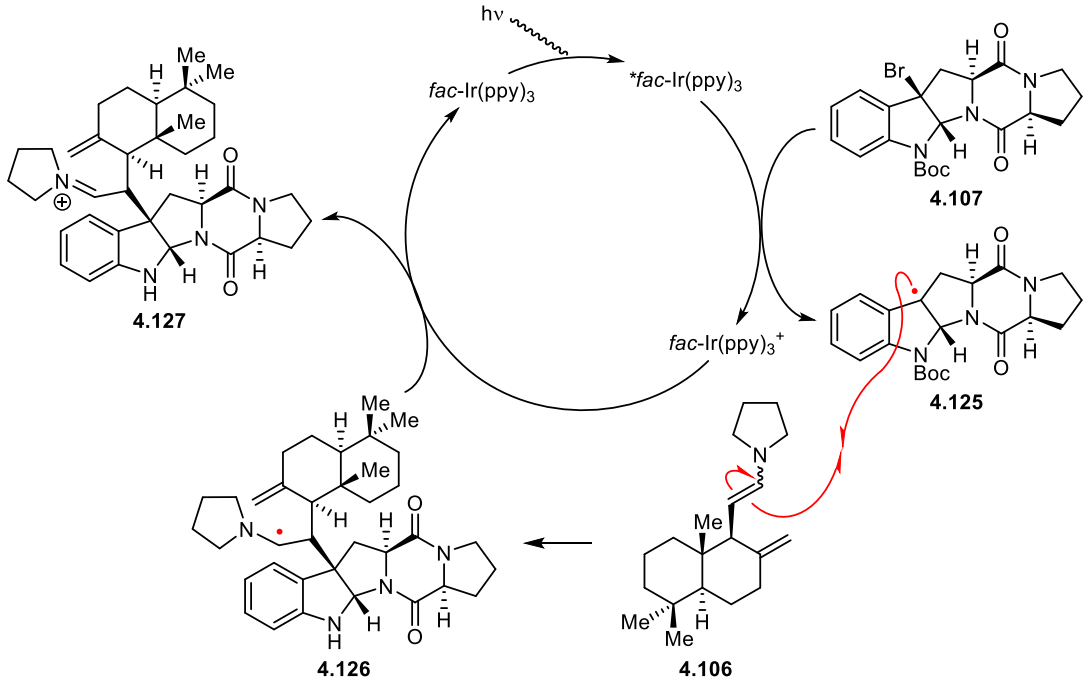

**Scheme 4.35** Asymmetric photoredox organocatalysis: a) α-alkylation of aldehydes; b) α-benzylation of aldehydes

This was expanded to the α-benzylation of electron-deficient aryl- and heteroaryl-substrates.[62] Excitation of *fac*-$Ir(ppy)_3$ with weak fluorescent light produced the strong reductant, $*$*fac*-$Ir(ppy)_3$, which was able to reduce benzyl bromide **4.122** directly using an oxidative quenching cycle. This eliminated the need for a sacrificial donor. These α-alkylation reactions were studied by DFT calculations.[63] The rate-determining step was determined to be the coupling of the electron-rich enamine and the electrophilic radical. Radical addition-oxidation was the determined to be the most favorable pathway for this step. This methodology has since been expanded to the asymmetric α-trifluoromethylation[64] and α-amination of aldehydes.[65] Furthermore, the photoredox organocatalyzed asymmetric α-alkylation of aldehydes now serves as a benchmark to test other photocatalysts including Eosin Y[66] and Rose Bengal.[67]

### 4.4.2 Photoredox Catalysis: Model Studies

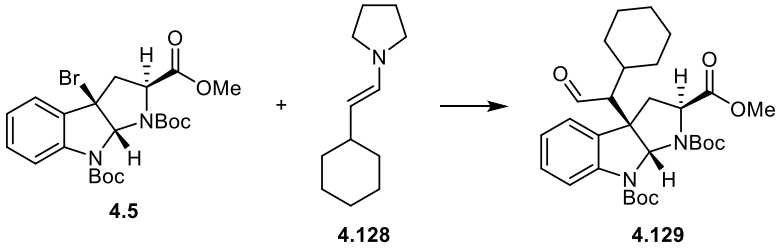
Based on the previously discussed examples, we thought the α-alkylation of enamine **4.106** via photoredox catalysis would be reasonable. Bromopyrroloindoline **4.107**, like (±)-**4.86** or **4.112**, should be sufficiently electron-deficient to engage in the photoredox cycle. As shown by the reductive dehalogenation by Stephenson et al.,[53] as well as the successful use of photoredox catalysis in the synthesis of drimentines A, F, and G,[1,68] epimerization at C2 of **4.107** should not occur. Because enantioselectivity is not required, we decided to use pyrrolidine to form the enamine with aldehyde **4.108**. Additionally, we decided to prepare the enamine stoichiometrically in advance in order to remove the necessity for an organocatalytic cycle.

We proposed that bromopyrroloindoline **4.107** would be reduced by the excited photoredox catalyst (Figure 4.30, shown with *fac*-Ir(ppy)$_3$) to radical **4.125** (Scheme 4.36). That would undergo coupling with enamine **4.106** to produce α-amino radical **4.126**. Reduction of *fac*-Ir(ppy)$_3^+$ would provide **4.127** and regenerate *fac*-Ir(ppy)$_3$.



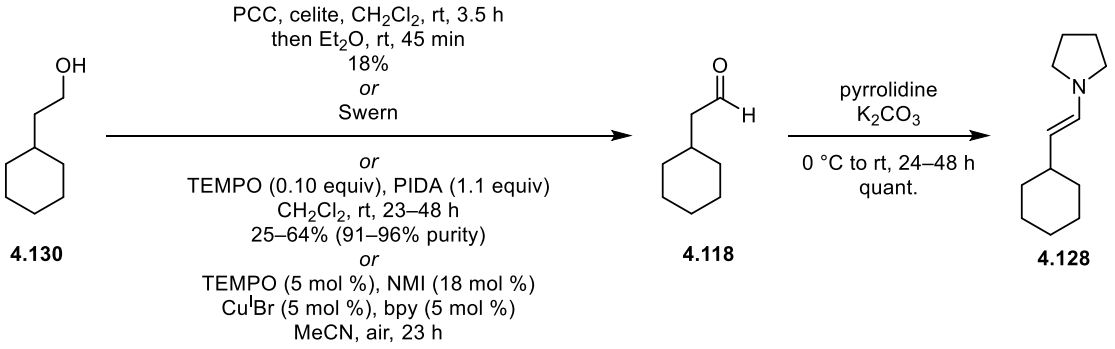

**Scheme 4.36** Proposed photoredox catalytic cycle

Like with reductive cross-coupling, we decided to test the photoredox α-alkylation using model substrates: bromopyrroloindoline **4.5** and enamine **4.128**, which would provide aldehyde **4.129** after hydrolysis (Scheme 4.37). The synthesis of **4.5** has been previously discussed (Scheme 4.20).




**Scheme 4.37** Model substrates for photoredox-catalyzed α-alkylation

Enamine **4.128** was prepared in two steps from 2-cyclohexylethanol **4.130**. Selective oxidation of **4.130** proved challenging due to its low molecular weight and volatility. Initially, pyridinium chlorochromate (PCC) oxidation was attempted following a literature procedure for its preparation (Scheme 4.38).[69] Stirring **4.130** with PCC and celite in $CH_2Cl_2$ at room temperature for 3.5 hours followed by stirring with $Et_2O$ at room temperature for 45 minutes produced a 1:1 mixture of **4.118** and the corresponding carboxylic acid. An acid-base workup removed the carboxylic acid to provide **4.118** in 18% yield; however, autooxidation of **4.118** continued. After 7 days, it was again a 1:1 mixture of **4.118** and carboxylic acid.




**Scheme 4.38** Synthesis of enamine **4.128**

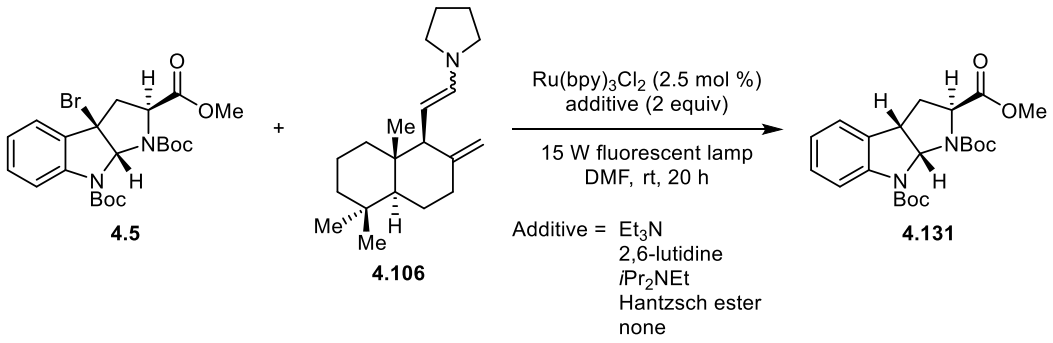
Next, Swern oxidation using dimethylsulfoxide (DMSO), oxalyl chloride, and triethylamine was attempted as it should not overoxidize **4.118** to the carboxylic acid.[70] Indeed, the reaction went to full conversion, and no carboxylic acid was produced. However, **4.118** was contaminated with additional byproducts that could not be removed by workup. Column chromatography was not attempted because a previous preparation of **4.118** mentioned that "silica gel appears to polymerize the product."[71]

Oxidation of **4.130** with TEMPO (0.10 equiv) and PIDA (1.1 equiv) in $CH_2Cl_2$ proceeded smoothly; aldehyde **4.118** was produced without any overoxidation. The superstoichiometric iodobenzene produced during the reaction was removed by a series of extractions whereby aldehyde **4.118** was converted to the bisulfite adduct then hydrolyzed. This provided **4.118** in 91–96% purity. However, the yields from this reaction ranged from 25 to 64%, presumably due to loss of material during the workup as **4.118** is highly volatile.

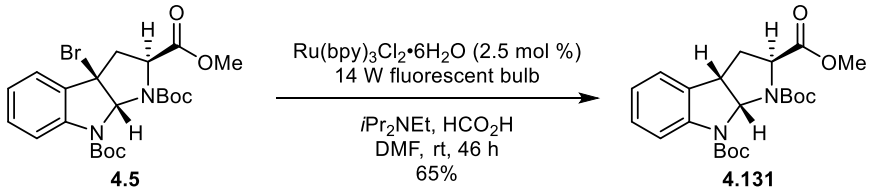
To remove the possibility of loss of material on workup, the TEMPO/PIDA conditions were changed to those developed by Stahl et al.[72] Alcohol **4.130** was aerobically oxidized using TEMPO (5 mol %), *N*-methyl imidazole (NMI, 10 mol %), $Cu^{I}Br$ (5 mol %), and bpy (5 mol %). The reaction was run closed with a balloon of air in order to minimize loss of product. Additionally, after stirring at room temperature for 4.5 hours, **4.130** was not completely consumed, so additional NMI (8 mol %) was added. All byproducts were removed by simple aqueous workup, and product loss during

concentration was minimized by keeping **4.118** in an ice bath. Enamine **4.128** was prepared quantitatively by stirring aldehyde **4.118** with pyrrolidine (1.1 equiv) and potassium carbonate neat.

The initial screening for reactivity in the photoredox-catalyzed α-alkylation was done by allowing model bromopyrroloindoline **4.5** to react with enamine **4.106** (Scheme 4.39). They were irradiated with a 15 W fluorescent lamp in the presence of $Ru(bpy)_3Cl_2$ (2.5 mol %) and a variety of additives (triethylamine, 2,6-lutidine, Hunig's base, and Hantzsch ester) in DMF for 20 hours. Unfortunately, the only product of the reactions was reduction byproduct **4.131**. Additionally, none of the reactions went to completion; **4.5**, **4.106**, and aldehyde **4.108** all remained. Reduction byproduct **4.131** was confirmed by independent synthesis from **4.5** using Stephenson's reductive dehalogenation procedure (Scheme 4.40).[53]



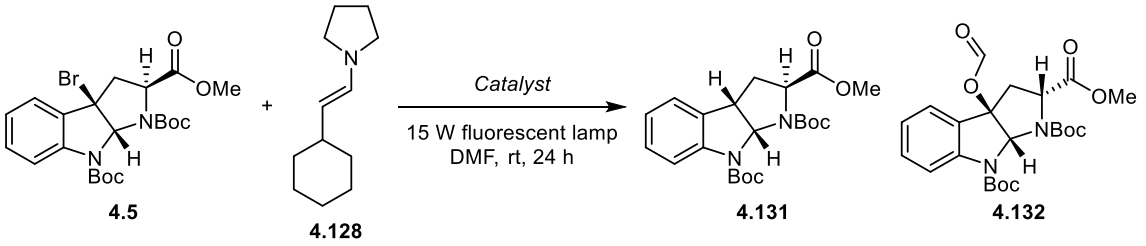

**Scheme 4.39** Initial photoredox-catalyzed α-alkylation reactions: screening of additives




**Scheme 4.40** Independent synthesis of reduction byproduct **4.131**

Cyclic voltammetry of **4.5** gave a first reduction potential of –0.800 eV.[§§] We realized that while the addition of amine bases was necessary to begin the reductive quenching cycle, they were also serving as hydrogen donors, leading to the preferential formation of reduction byproduct **4.131**. The removal of these hydrogen donors from the reaction conditions was necessary. Changing to *fac*-Ir(ppy)$_3$ allowed us to remove the amine bases because it is a strong enough reductant to directly reduce **4.5** (oxidative quenching cycle). So, the reactions between **4.5** and **4.128** using Ru(bpy)$_3$Cl$_2$ and *fac*-Ir(ppy)$_3$ were compared (Table 4.7). When irradiated with a 15 W fluorescent lamp in the presence of 2.5 mol % of catalyst in DMF for 24 hours, neither reaction went to completion. Additionally, the only product was **4.131**. However, when the loading of *fac*-Ir(ppy)$_3$ was increased (5.0 mol %), a new product resulted. This was determined to be formate ester **4.132**.

**Table 4.7** Screening of photoredox catalysts

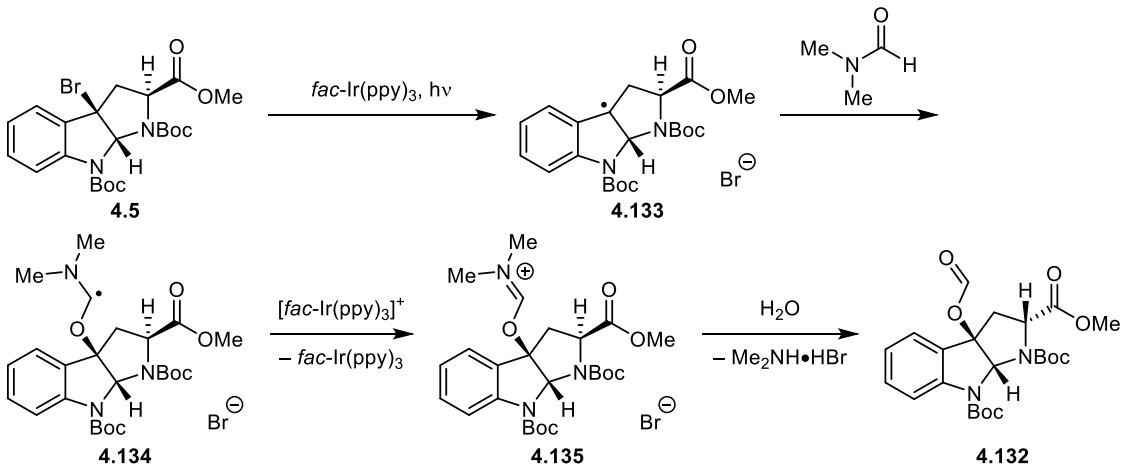



| Entry[a] | Catalyst | Loading (mol %) | Result[a] |
|---|---|---|---|
| 1 | Ru(bpy)$_3$Cl$_2$ | 2.5 | **4.131** |
| 2 | *fac*-Ir(ppy)$_3$ | 2.5 | **4.131** |
| 3 | *fac*-Ir(ppy)$_3$ | 5.0 | **4.131**, **4.132** |

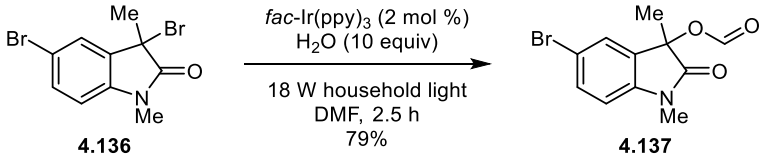
[a] Reactions prepared on the benchtop and degassed with $N_2$. [b] Reactions did not go to completion; bromopyrroloindoline **4.5** was recovered.

[§§] Cyclic voltammetry performed by Lafe Purvis. It was conducted in THF with a silver electrode and referenced to ferrocene.

A possible mechanism for the formation of formate ester **4.132** is shown in Scheme 4.41. DMF likely trapped bromopyrroloindoline radical **4.133**, which was produced by reduction of **4.5** by **fac*-Ir(ppy)$_3$. Resulting radical **4.134** would be oxidized by [*fac*-Ir(ppy)$_3$]$^+$ to regenerate the ground state catalyst and iminium ion **4.135**. Hydrolysis upon workup (saturated aqueous $NH_4Cl$) would provide product **4.132**. DMF has been demonstrated previously to be non-innocent in photoredox reactions. In 2014, Chen and Xiao et al.[73] reported the formyloxylation of 3-bromooxindoles (Scheme 4.36). Upon irradiation with an 18 W household lamp, bromooxindole **4.136** in the presence of *fac*-Ir(ppy)$_3$, DMF and water underwent formyloxylation to produce **4.137** in 79% yield.



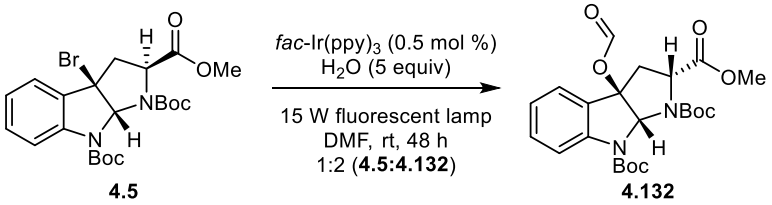

**Scheme 4.41** Possible mechanism for preparation of formate ester **4.132**




**Scheme 4.42** Photocatalytic formyloxylation reaction of 3-bromooxindole **4.136**

The formyloxylation of bromopyrroloindoline **4.5** was somewhat optimized. When the reactions were prepared on the benchtop and degassed with nitrogen, the ratio

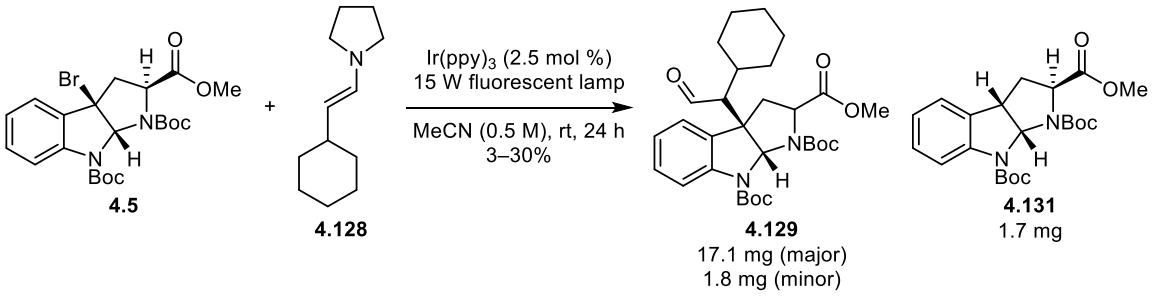
of starting bromide **4.5** to formate ester **4.132** remained at 22:1 after 48 hours. However, when the reactions were prepared in a nitrogen-filled glovebox, reactivity greatly improved. After 48 hours, the ratio of **4.5** to **4.132** was 1.5:1. This increase in reactivity was likely due to the absence of background decomposition pathways caused by $O_2$. Added water (5 equiv) further increased reactivity (Scheme 4.37), producing a 1:2 mixture of **4.5** and **4.132** within 48 hours. NMR spectroscopic experiments (COSY, nOe) determined that **4.132** was the *endo*-isomer; C2-epimerization had occurred.




**Scheme 4.43** Optimization of reaction to prepare formate ester **4.132**

Having realized that the solvent could be non-innocent in photoredox reactions, a solvent screen was undertaken. Tetrahydrofuan, 1,4-dioxane, *N*,*N*-dimethylformamide, dimethylsulfoxide, acetonitrile, chloroform, and toluene were tested. As before, DMF was non-innocent. The catalyst, *fac*-Ir(ppy)$_3$, suffered from low solubility; it was only soluble in DMF, DMSO, and $CH_2Cl_2$, and it was sparingly soluble in MeCN. When **4.5** and **4.128** (5 equiv) were irradiated with 15 W fluorescent light in the presence of Ir(ppy)$_3$ (2.5 mol %) in MeCN for 24 hours, new products began to form (Scheme 4.44). These three new products had peaks in the $^1$H NMR spectrum between 9.0 and 10.0 ppm, all doublets, and were likely diastereomers. They had a *m/z* of 565.2723, which corresponded to the chemical formula $[C_{30}H_{42}N_2O_4 + Na]^+$. NMR spectroscopic experiments ($^1$H, COSY, HMQC, and HMBC) determined that alkylation had occurred at C3a. The chemical shifts of the methyl esters were all between 3.60 and 3.65 ppm. Pyrroloindoline *endo*-isomers typically have the $^1$H NMR peak of the ester shifted significantly upfield (~3.10 ppm).[3] Therefore, these were assigned as the *exo*-diasteromers. The mixture of diastereomers was isolated in 3–30% yield depending on

how the reaction had been set up. Because the solubility of *fac*-Ir(ppy)$_3$ was poor, attempting to prepare a stock solution of it in MeCN led to decreased reactivity.

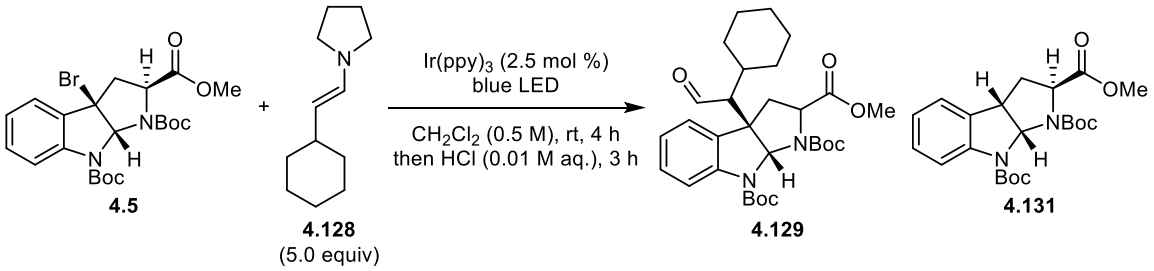



**Scheme 4.44** Identification of pyrroloindoline **4.129**

The solvent was changed to $CH_2Cl_2$, which provided better solubility for the photocatalyst. Additionally, when the light source was changed from a 14 W fluorescent lamp to a blue LED lightbulb, the reactivity improved to 75% conversion within 23 hours. Changing to a blue LED ropelight allowed for 83% conversion of **4.5** in 4 hours as determined by qNMR spectroscopy (using 1,3,5-trimethoxybenzene as an internal standard). However, qNMR spectroscopy was performed after workup (saturated aqueous $NH_4Cl$), and the mass balance ranged from 11–48%, which was a point of concern. So, the reaction was prepared in a sealed NMR tube and monitored over 23 hours. Minimal amounts of aldehyde **4.129** were produced; however, a new broad peak appeared in the aldehyde region. High-resolution mass spectrometry of the crude reaction mixture determined that it was the iminium ion (*m/z* 596.3703). Likely, the low mass balance was being caused by incomplete hydrolysis of this iminium ion leading to product loss during workup. When the reaction mixture was stirred with aqueous hydrochloric acid (0.01 M) for 3 hours after completion of the photoredox reaction, mass balance was no longer an issue. Two additional catalysts were tested, *fac*-Ir(fppy)$_3$ and *fac*-Ir(tbbpy)$_3$, in the hope of improving catalyst solubility while also maintaining an oxidative quenching cycle. These reactions were conducted in sealed NMR tubes and were followed by qNMR. As the reducing power of the catalyst increased, the conversion increased. Additionally, a

5:1 ratio between **4.129** and **4.131** was maintained.

**Table 4.8** Photocatalyst screening for α-alkylation model reaction

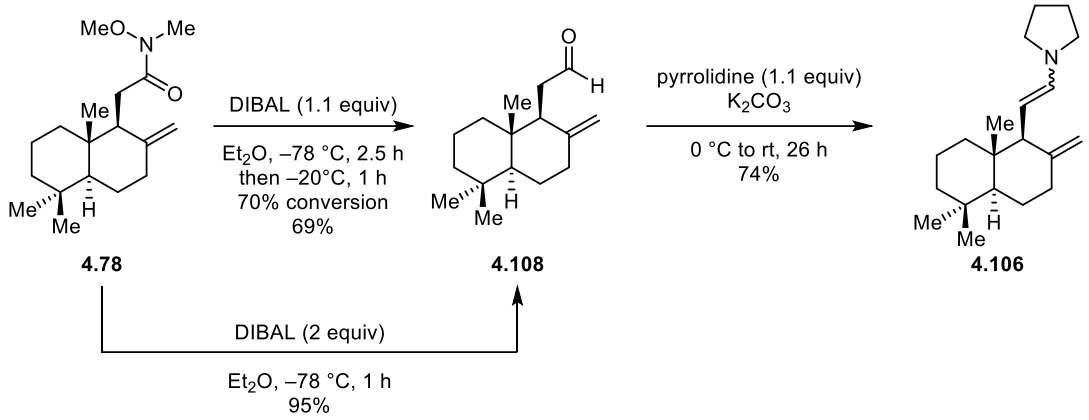



| Entry | Catalyst | **4.5** : **4.129** : **4.131**[a] |
|---|---|---|
| 1 | *fac*-Ir(fppy)$_3$ | 1 : 4.7 : 1 |
| 2 | *fac*-Ir(tbppy)$_3$ | 1 : 6.9 : 1.4 |
| 3 | *fac*-Ir(ppy)$_3$ | 1 : 11 : 2.3 |

[a] Determined by qNMR using 1,3,5-trimethoxybenzene. Integration of **4.129** indirectly determined based on integration of **4.128**.

### 4.4.3 Progress Towards Total Synthesis of Drimentine C

Enamine **4.106** was prepared from (+)-sclareolide. As before, lactone ring-opening to the Weinreb amide with subsequent dehydration, previously discussed in Chapter 3, provided olefin **4.78**.[42] Aldehyde **4.108** was prepared by DIBAL reduction of Weinreb amide **4.78** according to the procedure by Boukouvalas et al (Scheme 4.45).[42] However, this reproducibly led to only 70% conversion of starting material. Instead, when DIBAL was used in excess (2 equiv), the reaction went to completion within 1 hour at –78 °C, and was isolated in 95% yield. Stirring aldehyde **4.108** with pyrrolidine (1.1 equiv) at room temperature for 26 hours provided enamine **4.106** in 74% yield. The enamine could be used without purification, but could also be purified by column chromatography.



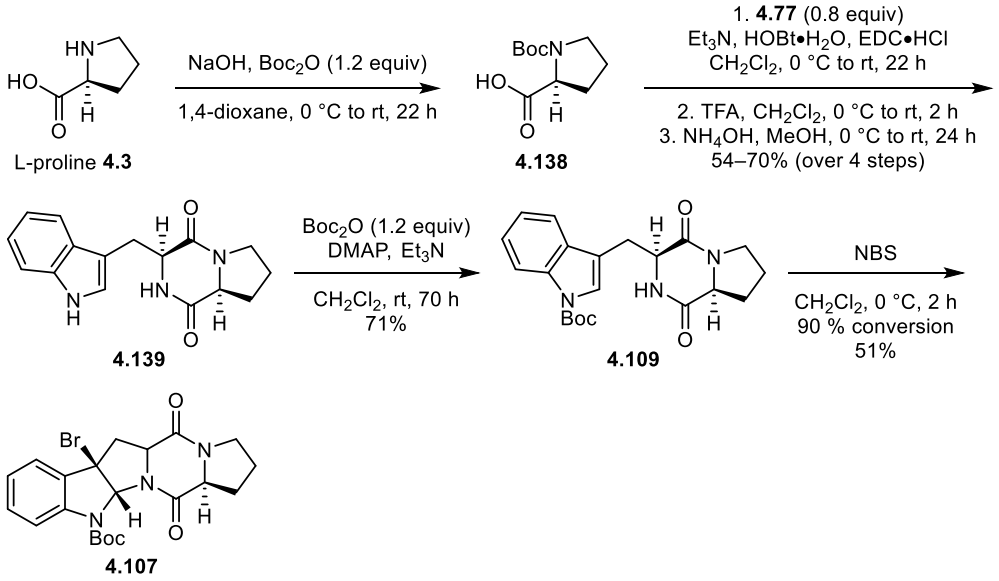

**Scheme 4.45** Preparation of enamine **4.106**

Bromopyrroloindoline **4.107** was prepared in six steps from L-proline (**4.3**). Boc-protection provided **4.138**, which was carried into the following set of reactions without purification. Diketopiperazine formation of **4.138** with L-tryptophan methyl ester **4.77** required three steps: peptide coupling, deprotection, and condensation-cyclization. Diketopiperazine **4.139** was isolated in 54–70% yield after recrystallization from methanol.

Mono-protection of the indole nitrogen of **4.139** required some optimization. Reaction with $Boc_2O$ (3 equiv), sodium hydroxide, and $Bu_4NHSO_4$ at room temperature for 2 hours provided the bis-protected diketopiperazine as the sole product. The same conditions using only a slight excess of $Boc_2O$ (1.2 equiv) provided a complex mixture of the mono- and bis-protected products. Finally, when the conditions were modified to using triethylamine and catalytic DMAP, the reaction was very slow, requiring 70 hours, but mono-protected **4.109** was isolated as the sole product.

Bromocyclization using standard conditions, NBS and PPTS at room temperature for 22 hours, provided a mixture of *exo*- and *endo*-diastereomers. In fact, both diastereomers were present within 2 hours. The stereochemistry of the *endo*-isomer was determined by a combination of NMR experiments, including NOESY. Because the *exo*-isomer should be favored kinetically, the reaction was carried out at –30 °C without the acid catalyst. However, no reaction was observed. When the temperature was increased

to 0 °C, the bromocyclization went to 90% completion, yielding a single diastereomer (not *endo*) in 51% yield. NOESY on this isomer was not definitive, and crystallization experiments are underway.

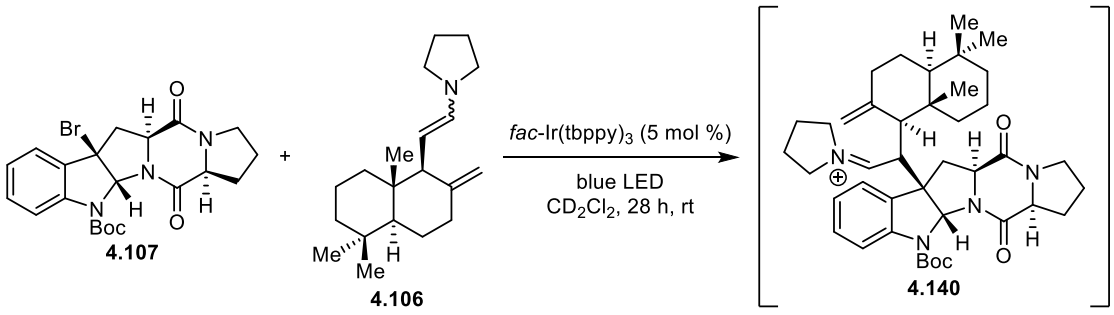



**Scheme 4.46** Synthesis of bromopyrroloindoline **4.107**

Initial reaction of bromopyrroloindoline **4.107** and enamine **4.106** (3.8 equiv) by blue LED irradiation with *fac*-Ir(ppy)$_3$ (2 mol %) in $CD_2Cl_2$ for 28.5 hours provided a new product with the chemical formula $C_{38}H_{54}N_2O_7$, as determined by high resolution mass spectrometry. However, after three columns, the product had decomposed. Additional reactions also produced this product, but all attempts to isolate it by column chromatography proved unsuccessful; only bromopyrroloindoline **4.107** and aldehyde **4.108** were recovered. When reactions were run using *fac*-Ir(ppy)$_3$ at 0.5 M, the catalyst did not fully dissolve in $CD_2Cl_2$ and no product was observed. So, the catalyst was changed to *fac*-Ir(tbppy)$_3$, which had better solubility, and the reactions were run at slightly higher dilution (0.4 M). However, these trials, which were set-up in a nitrogen-filled glovebox in sealed NMR tubes, showed no enamine prior to irradiation. Instead, the corresponding aldehyde **4.108** was present, meaning that the enamine had hydrolyzed in

the reaction. The solvent was found to be contaminated with water. A new bottle of $CD_2Cl_2$ was obtained and dried over 3Å molecular sieves.

Using the dried $CD_2Cl_2$, bromopyrroloindoline **4.107** and enamine **4.106** (1.5 equiv) with *fac*-Ir(tbppy)$_3$ were irradiated with blue LED at room temperature for 28 hours. Within that time, **4.107** was fully consumed, and iminium ion **4.140** (as determined by $^1$H NMR spectroscopy and mass spectrometry; structure not confirmed) was present. By $^1$H NMR spectroscopy, the exocyclic olefin is still present. Attempts to hydrolyze the iminium ion using aqueous hydrochloric acid (0.1 M) resulted in no change, presumably because the pH (4) was favorable for an iminium ion. So, the pH was raised to 8 with aqueous disodium hydrogen phosphate (0.1 M) and the reaction mixture was heated at 35 °C, stirring vigorously, for 6.5 hours; however, **4.140** did not completely hydrolyze. TLC-MS showed that the iminium ion was close to the baseline along with a new product. If the new product is the desired product, it is much more polar than expected and could explain why the product had not been isolated up to this point. Isolation, characterization, and optimization are ongoing.




**Scheme 4.47** NMR tube photoredox-catalyzed α-alkylation of **4.106** with **4.107**

## 4.5 Concluding Remarks

For the convergent synthetic route to drimentine C (**4.1**, Scheme 4.1), the key disconnection is between the pyrroloindoline core and the sesquiterpene. Three methodologies for preparing this C–C bond have been investigated. The first

methodology, organocuprate addition into cyclopropylazetoindoline **4.9** (Scheme 4.2), was abandoned because it would result in epimerization at C2 to the undesired *endo*-pyrroloindoline. Nickel-catalyzed reductive cross-coupling, the second methodology (Scheme 4.14), was abandoned because alkylation occurred at the aromatic ring of model substrate **4.86** resulting in indole **4.101**. The third methodology, photoredox-catalyzed α-alkylation of enamine **4.106** (Scheme 4.31) has produced promising results. Completion of the synthesis from key intermediate **4.105** will involve deformylation, either directly or via Pinnick oxidation and Barton decarboxylation, and global deprotection.

## References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# Experimental

## General Details

Unless otherwise indicated, all reactions were carried out using either flame-dried or oven-dried glassware under a nitrogen atmosphere. Dichloromethane ($CH_2Cl_2$), toluene (PhMe), and acetonitrile (MeCN) were distilled from $CaH_2$ prior to use. Tetrahydrofuran (THF) was distilled from sodium/benzophenone prior to use. Benzene, methanol (MeOH), anhydrous *N*,*N*-dimethylacetamide, anhydrous *N*,*N*-dimethylformamide (DMF), and anhydrous diethyl ether ($Et_2O$) were purchased from Sigma-Aldrich and Alfa Aesar and used without further purification.

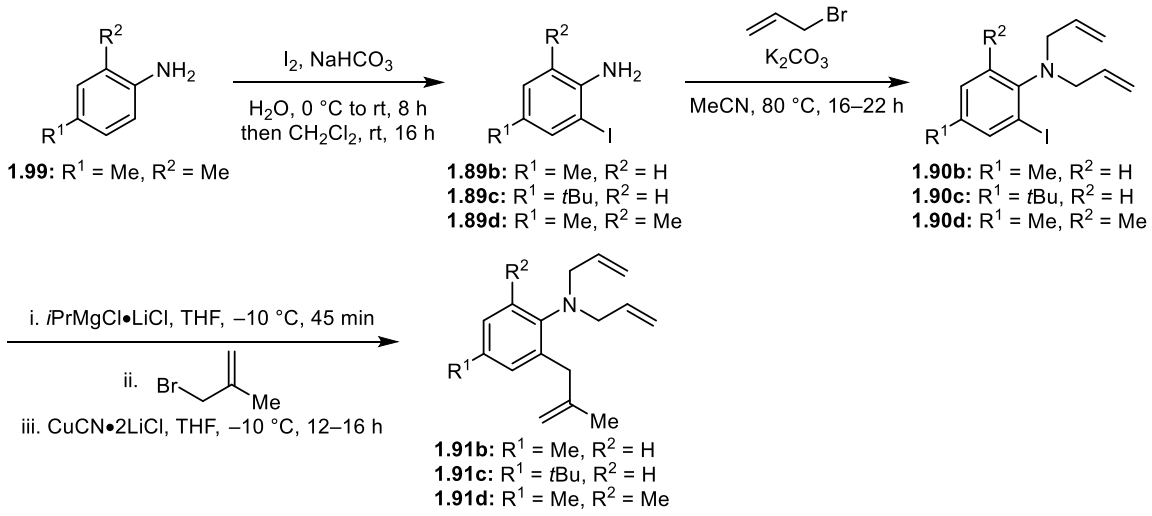
Unless otherwise indicated, all chemicals were purchased from commercial sources (Acros Organics, Alfa Aesar, Oakwood Chemical, Sigma-Aldrich, and TCI America) and used as received. All transition metal complexes were purchased from Sigma-Aldrich or Strem and used as received. Triphenylborane ($BPh_3$) was purchased from Sigma-Aldrich and recrystallized from anhydrous heptanes under nitrogen.[1] Tris(pentafluorophenyl)borane ($B(C_6F_5)_3$) was purchased from Alfa Aesar or Strem and used as received. 1-oxa-2-oxo-3-thiaindolizinium chloride was purchased from TCI America and used as received. Unless otherwise indicated, all $B(C_6F_5)_3$-promoted or palladium-catalyzed aminocyanation reactions, nickel-catalyzed reductive cross-coupling reactions, and nickel- or iridium-catalyzed photoredox reactions were prepared in a Vacuum Atmospheres nitrogen-filled glove box in 0.5- or 1-dram vials (ChemGlass) with PTFE lined caps and heating was applied by aluminum block heaters. Microwave reactions were carried out in a Biotage Initiator 2.0 reactor. Photoredox reactions were conducted using a 14 or 15 W fluorescent light bulb, a 15 W blue light bulb, or a blue LED rope light. An external fan was used to keep the reactions at room temperature.

[1] Köster, R.; Binger, P.; Fenzl, W. *Inorg. Synth.* **1974**, *15*, 134.

Analytical thin-layer chromatography (TLC) and preparative thin-layer chromatography were carried out using 250 μm and 1000 μm silica plates (SiliCycle), respectively. Eluted plates were visualized first with UV light (254 nm) and then by staining with ceric sulfate/molybdic acid or potassium permanganate/potassium carbonate, followed by heating. Flash chromatography was performed using 230 – 400 mesh (particle size 40 – 63 μm) silica gel purchased from SiliCycle unless otherwise indicated. When indicated, flash chromatography was performed using Premium Rf (particle size 20 – 45 μm) silica gel purchased from Sorbtech.

$^{1}$H NMR (300, 400, and 500 MHz) and $^{13}$C NMR (75, 100, and 125 MHz) spectra were obtained on Varian Inova and Bruker Avance III instruments. $^{1}$H NMR spectra are reported as δ values in ppm relative to tetramethylsilane (TMS) (δ 0.00) if collected in $CDCl_3$ or $CD_2Cl_2$ or dimethylsulfoxidechloride (δ 2.50) if collected in DMSO-$d_6$. $^{13}$C NMR spectra are reported as δ values in ppm relative to chloroform (δ 77.00) if collected in $CDCl_3$, dichloromethane (δ 53.41) if collected in $CD_2Cl_2$, or dimethyl sulfoxidechloride (δ 39.50) if collected in DMSO-$d_6$. $^{1}$H NMR coupling constants are reported in Hz; multiplicity is indicated as follows: s (singlet), d (doublet); t (triplet); q (quartet); quint (quintet); m (multiplet); dd (doublet of doublets); ddd (doublet of doublet of doublets); dddd (doublet of doublet of doublet of doublets); dt (doublet of triplets); td (triplet of doublets); ddt (doublet of doublet of triplets); app (apparent); br (broad). Infrared (IR) spectra were obtained on a MIDAC FT-IR spectrometer. Thin-film samples were prepared by evaporating solvent ($CH_2Cl_2$ or $CDCl_3$) on NaCl plates. Low-resolution mass spectra (LRMS) in EI or CI experiments were performed on a Varian Saturn 2200 GC-MS system. LRMS and high-resolution mass spectra (HRMS) in electrospray (ESI) experiments were performed on a Bruker BioTOF II instrument using PEG-300, PEG-400, PPG-425, or PPG-725 as an internal standard.

**Experimental Section for Part I**




**1.99:** $R^1$ = Me, $R^2$ = Me

**1.89b:** $R^1$ = Me, $R^2$ = H
**1.89c:** $R^1$ = *t*Bu, $R^2$ = H
**1.89d:** $R^1$ = Me, $R^2$ = Me

**1.90b:** $R^1$ = Me, $R^2$ = H
**1.90c:** $R^1$ = *t*Bu, $R^2$ = H
**1.90d:** $R^1$ = Me, $R^2$ = Me

**1.91b:** $R^1$ = Me, $R^2$ = H
**1.91c:** $R^1$ = *t*Bu, $R^2$ = H
**1.91d:** $R^1$ = Me, $R^2$ = Me

Anilines **1.89b** and **1.89c** were prepared following known procedures.[2] The THF solution of *i*PrMgCl·LiCl was prepared following a known procedure.[3]

**2-Iodo-4,6-dimethylaniline 1.89d**[4]

To 2,4-dimethylaniline (1.23 mL, 10.0 mmol, 1.0 equiv) and sodium bicarbonate (1.27 g, 15.0 mmol, 1.5 equiv) in $H_2O$ (10.0 mL) at 0 °C was added $I_2$ (2.79 g, 11.0 mmol, 1.1 equiv). The reaction mixture was allowed to warm to room temperature while stirring, open to air, for 8 h. At this point TLC analysis (3:2 EtOAc/hexanes) indicated that the reaction was not complete. $CH_2Cl_2$ (1.0 mL) was added, and the reaction mixture was allowed to stir at room temperature for an additional 16 hours. At this point, TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with $Et_2O$ (100.0 mL), and 40% aqueous $NaHSO_3$ (w/w) (1.3 mL) was added. The organic layer was separated, dried over $Na_2SO_4$, filtered, and concentrated. **1.89d** was used for the next step without further purification.

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[2] **6b**: Xiao, W. J.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646. **6c**: Shirtcliff, L. D.; Weakley, T. J. R.; Haley, M. M. *J. Org. Chem.* **2004**, *69*, 6979.
[3] Krasovkiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333.
[4] Procedure was modified from: Ishida, T.; Kikuchi, S.; Tsubo, T.; Yamada, T. *Org. Lett.* **2013**, *15*, 848.

***N,N*-Diallyl-2-iodo-4-methylaniline 1.90b**[5]

To a nitrogen-flushed flask were added **1.89b** (1.17 g, 5.0 mmol, 1.0 equiv), potassium carbonate (2.76 g, 20.0 mmol, 4.0 equiv), allyl bromide (1.73 mL, 20.0 mmol, 4.0 equiv), and MeCN (10.0 mL). The resulting suspension was vigorously stirred at 80 °C for 16 h at which point TLC analysis (1:3 EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixtures were combined, diluted with $CH_2Cl_2$, and extracted with $H_2O$ (10 mL). The aqueous phase was back-extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to give **1.90b** as a dark red oil. **1.90b** was diluted with benzene (2.0 mL), concentrated again, and used for the next step without further purification.

***N,N*-Diallyl-4-(*tert*-butyl)-2-iodoaniline 1.90c**

To a nitrogen-flushed flask were added **1.89c** (1.39 g, 5.0 mmol, 1.0 equiv), potassium carbonate (2.76 g, 20.0 mmol, 4.0 equiv), allyl bromide (1.73 mL, 20.0 mmol, 4.0 equiv), and MeCN (10.0 mL). The resulting suspension was vigorously stirred at 80 °C for 18 h at which point TLC analysis (1:3 EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixtures were combined, diluted with $CH_2Cl_2$, and extracted with $H_2O$ (10 mL). The aqueous phase was back-extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to give **1.90c** as a light orange oil. **1.90c** was diluted with benzene (2.0 mL), concentrated again, and used for the next step without further purification.

***N,N*-Diallyl-2-iodo-4,6-dimethylaniline 1.90d**

To a nitrogen-flushed flask was added **1.89d** (~7.7 mmol, 1.0 equiv), potassium carbonate (5.29 g, 38.2 mmol, 5.0 equiv), allyl bromide (3.31 mL, 38.2 mmol, 5.0 equiv),

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[5] Procedure was modified from: Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934.

and MeCN (15.3 mL). The reaction mixture was vigorously stirred at 75 °C for 22 h at which TLC analysis (1:3 EtOAc/hexanes) indicated complete consumption of starting material. The reaction mixture was diluted with $CH_2Cl_2$ and filtered through a short (4 – 5 cm) silica gel column. The resulting solution was concentrated *in vacuo* to give **1.90d**, which was diluted with benzene (2.0 mL), concentrated again, and used for the next step without further purification.

***N,N*-diallyl-4-methyl-2-(2-methylallyl)aniline 1.91b**[6]

A flame-dried flask was charged with crude **1.90b** (neat, ~4.6 mmol, 1.0 equiv) and cooled to –10 °C under $N_2$. *i*PrMgCl•LiCl (0.76 M in THF, 7.2 mL, 5.5 mmol, 1.2 equiv) was slowly added via syringe. The resulting solution was stirred at –10 °C for 45 min at which point 3-bromo-2-methyl-1-propene (0.58 mL, 5.9 mmol, 1.3 equiv) and CuCN•2LiCl (1.0 M in THF, 0.23 mL, 0.23 mmol, 0.05 equiv) were sequentially added at –10 °C. The reaction was allowed to warm to room temperature over the course of 12 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (10 mL), diluted with $H_2O$, and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting mixture was purified by flash column chromatography (1:5 $CH_2Cl_2$/hexanes) to give **1.91b** as a colorless oil (832 mg, 3.4 mmol, 69% yield over two steps). $R_f$ = 0.29 (2:98 $CH_2Cl_2$/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.96 – 6.95 (m, 2H), 5.78 (ddt, *J* = 16.6, 10.3, 6.4 Hz, 2H), 5.14 (ddd, *J* = 17.1, 3.4, 1.5 Hz, 2H), 5.07 (ddd, *J* = 10.3, 3.4, 1.5 Hz, 2H); 4.82 (m, 1H), 4.65 (m, 1H), 3.51 (dt, *J* = 6.2, 1.5 Hz, 4H), 3.43 (s, 2H), 2.28 (s, 3H), 1.71 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 147.4, 145.7, 135.6, 135.5, 132.9, 131.0, 126.9, 122.6, 116.9, 111.5, 56.7, 38.6, 22.7, 20.9; **HRMS** (ESI) calcd for $[C_{17}H_{23}N + H]^+$ 242.1903, found 242.1912.

[6] Procedure was modified from: Yip, K. T.; Yang, M.; Law, K. L.; Zhu, N. Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130. Also see ref. 3.

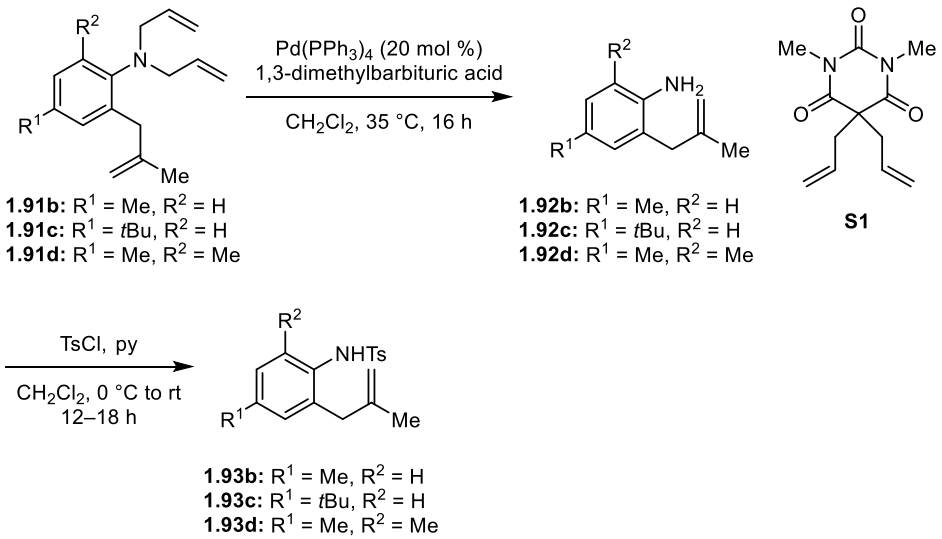
***N,N*-diallyl-4-*tert*-butyl)-2-(2-methylallyl)aniline 1.91c**

A flame-dried flask was charged with crude **1.90c** (neat, ~4.3 mmol, 1.0 equiv) and cooled to –10 °C under $N_2$. *i*PrMgCl•LiCl (0.76 M in THF, 6.8 mL, 5.2 mmol, 1.2 equiv) was slowly added via syringe. The resulting solution was stirred at –10 °C for 45 min at which point 3-bromo-2-methyl-1-propene (0.55 mL, 5.6 mmol, 1.3 equiv) and CuCN•2LiCl (1.0 M in THF, 0.22 mL, 0.22 mmol, 0.05 equiv) were sequentially added at –10 °C. The reaction was allowed to warm to room temperature over the course of 12 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (10 mL), diluted with $H_2O$, and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting mixture was purified by flash column chromatography (1:5 $CH_2Cl_2$/hexanes) to give **1.91c** as a light yellow oil (841 mg, 3.0 mmol, 59% yield over two steps). $R_f$ = 0.22 (2:98 $CH_2Cl_2$/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 2.4 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.4 Hz, 1H); 6.97 (d, *J* = 8.3 Hz, 1H), 5.78 (ddt, *J* = 16.5, 10.2, 6.1 Hz, 2H), 5.15 (ddd, *J* = 17.6, 3.4, 1.5 Hz, 2H), 5.08 (ddd, *J* = 10.3, 3.4, 1.5 Hz, 2H), 4.81 (m, 1H), 4.62 (m, 1H), 3.52 (d, *J* = 5.8 Hz, 4H), 3.44 (s, 2H), 1.72 (s, 3H), 1.28 (s, 9H); **$^{13}$C NMR** (125 MHz, $CD_2Cl_2$) δ 147.4, 145.9, 145.87, 135.8, 134.7, 127.6, 122.9, 121.9, 116.4, 111.1, 56.5, 38.7, 34.0, 31.1, 22.5; **HRMS** (ESI) calcd for $[C_{20}H_{29}N + H]^+$ 284.2373, found 284.2364.

***N,N*-diallyl-2,4-dimethyl-6-(2-methylallyl)aniline 1.91d**

A flame-dried flask was charged with crude **1.90d** (neat, ~6.9 mmol, 1.0 equiv) and cooled to –16 °C under $N_2$. *i*PrMgCl•LiCl (1.4 M in THF, 5.9 mL, 5.9 mmol, 1.2 equiv) was slowly added via syringe. The resulting solution was stirred at –25 °C for 45 min at which point 3-bromo-2-methyl-1-propene (0.95 mL, 9.6 mmol, 1.4 equiv) and CuCN•2LiCl (1.0 M in THF, 0.35 mL, 0.35 mmol, 0.05 equiv) were sequentially added at –16 °C. The reaction was allowed to warm to room temperature over the course of 16 h. The reaction was quenched by addition of saturated aqueous $NH_4Cl$ (15 mL), diluted with $H_2O$, and extracted with $Et_2O$ (5 x 20 mL). The combined organic extracts were

washed with brine, dried over $MgSO_4$, filtered, and concentrated. The resulting mixture was purified by flash column chromatography (1:4 $CH_2Cl_2$/hexanes) to give **1.91d** as a colorless oil (1.16 g, 4.5 mmol, 53% yield over three steps). $R_f$ = 0.50 (1:4 $CH_2Cl_2$/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.83 (s, 2H), 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 2H), 5.08 (dd, *J* = 17.1, 1.6 Hz, 2H), 5.00 (dd, *J* = 10.0, 0.9 Hz, 2H), 4.84 (s, 1H), 4.60 (s, 1H), 3.65–3.54 (m, 4H), 3.40 (s, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.72 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 145.7, 145.6, 138.7, 137.3, 137.0, 134.5, 129.9, 128,4, 115.9, 111.9, 56.5, 40.0. 22.8, 20.8. 19.7; **HRMS** (ESI) calcd for $[C_{18}H_{25}N + H]^+$ 256.2060, found 256.2070.




**4-Methyl-2-(2-methylallyl)aniline 1.92b**[7]

In a nitrogen-filled glove box, a 20-mL vial was charged with tetrakis(triphenylphosphine)palladium(0) (81.4 mg, 0.07 mmol, 2.0 mol %), amine **1.91b** (831 mg, 3.4 mmol, 1.0 equiv), 1,3-dimethylbarbituric acid (3.25 g, 20.8 mmol, 6.0 equiv) and degassed $CH_2Cl_2$ (8.5 mL). The reaction mixture was sealed with a PTFE-lined cap, removed from the glove box and stirred at 35 °C for 17 h. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ (60 mL) and vigorously washed with 1 M

[7] Procedure was modified from: Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

aqueous NaOH (50 mL). The aqueous phase was back-extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to give an orange oil, which was an inseparable mixture of aniline **1.92b** and 5,5-diallyl-1,3-dimethyl-pyrimidine-2,4,6-trione (**S1**).[8] The crude product was used without additional purification.

**4-(*tert*-butyl)-2-(2-methylallyl)aniline 1.92c**

In a nitrogen-filled glove box, a 20-mL vial was charged with tetrakis(triphenylphosphine)palladium(0) (74.3 mg, 0.06 mmol, 2.0 mol %), amine **1.91c** (840 mg, 3.0 mmol, 1.0 equiv), 1,3-dimethylbarbituric acid (2.79 g, 17.8 mmol, 6.0 equiv) and degassed $CH_2Cl_2$ (7.5 mL). The reaction mixture was sealed with a PTFE-lined cap, removed from the glove box and stirred at 35 °C for 17 h. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ (60 mL) and vigorously washed with 1 M aqueous NaOH (50 mL). The aqueous phase was back-extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to give an orange oil, which was an inseparable mixture of the aniline **1.92c** and **S1**. The crude product was used without additional purification.

**2,4-Dimethyl-6-(2-methylallyl)aniline 1.92d**

In a nitrogen-filled glove box, a 20-mL vial was charged with tetrakis(triphenylphosphine)palladium(0) (13.9 mg, 0.01 mmol, 0.3 mol %), amine **1.91d** (1.02 g, 4.0 mmol, 1.0 equiv), 1,3-dimethylbarbituric acid (3.74 g, 24.0 mmol, 6.0 equiv) and degassed $CH_2Cl_2$ (10.0 mL). The reaction mixture was sealed with a PTFE-lined cap, removed from the glove box and stirred at 36 °C for 23 h. After cooling, the reaction mixture was diluted with $CH_2Cl_2$ (30 mL) and vigorously washed with 1 M aqueous NaOH (3 x 20 mL). The aqueous phase was back-extracted with $CH_2Cl_2$ (20 mL). The

[8] Identified by $^1$H NMR of the crude mixture. Also see: Kumarassamny, E.; Sivaguru, J. *Chem. Commun.* **2013**, *49*, 4346.

combined organic extracts were washed with brine (20 mL), dried over $Na_2SO_4$, filtered, and concentrated *in vacuo* to give an orange oil, which was an inseparable mixture of the aniline **1.92d** and **S1**. The crude product was used without additional purification.

**4-Methyl-*N*-(4-methyl-2-(2-methylallyl)phenyl)benzenesulfonamide 1.93b**

To a stirred solution of **1.92b** (~3.4 mmol, 1.0 equiv) and *p*-toluenesulfonyl chloride (785 mg, 4.1 mmol, 1.2 equiv) in $CH_2Cl_2$ (7.0 mL) at 0 °C was added pyridine (0.56 mL, 6.9 mmol, 2.0 equiv). The reaction was allowed warm to room temperature over 16 h. The reaction mixture was diluted with $H_2O$ (30 mL) and extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by flash column chromatography (5:95 EtOAc/hexanes) to give sulfonamide **1.93b** as a viscous, yellow oil (727 mg, 2.3 mmol, 67% yield over two steps). $R_f$ = 0.18 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.59 (dt, *J* = 8.5, 1.9 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 6.98 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.84 (d, *J* = 1.5 Hz, 1H), 6.72 (s, 1H), 4.83 (app s, 1H), 4.56 (m, 1H), 2.86 (s, 2H), 2.36 (s, 3H), 2.24 (s, 3H), 1.55 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 143.8, 143.6, 136.9, 135.9, 132.6, 131.7, 131.5, 129.5, 128.3, 127.0, 124.8, 112.6, 40.8, 22.2, 21.5, 20.9; **HRMS** (ESI) calcd for $[C_{18}H_{21}NO_2S + Na]^+$ 338.1191, found 338.1187.

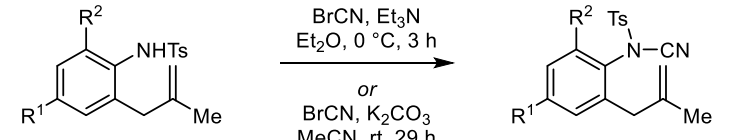
***N*-(4-(*tert*-butyl)-2-(2-methylallyl)phenyl)-4-methylbenzenesulfonamide 1.93c**

To a stirred solution of **1.92c** (~3.0 mmol, 1.0 equiv) and *p*-toluenesulfonyl chloride (691 mg, 3.6 mmol, 1.2 equiv) in $CH_2Cl_2$ (6.0 mL) at 0 °C was added pyridine (0.48 mL, 5.9 mmol, 2.0 equiv). The reaction was allowed to warm to room temperature over 16 h. The reaction mixture was diluted with $H_2O$ (30 mL) and extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by flash column chromatography (5:95 EtOAc/hexanes) to give sulfonamide **1.93c** as a white, waxy solid (509 mg, 1.4 mmol, 28% yield over two steps). $R_f$ = 0.13 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.61 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.19 (m, 3H), 7.03 (d, *J* =

2.4 Hz, 1H), 6.63 (s, 1H), 4.85 (m, 1H), 4.58 – 4.57 (m, 1H), 2.92 (s, 2H), 2.39 (s, 3H), 1.58 (s, 3H), 1.26 (s, 9H); **$^{13}$C NMR** (125 Mz, $CDCl_3$) δ 148.9, 143.8, 143.5, 137.1, 132.5, 131.0, 129.5, 127.9, 127.0, 124.5, 124.0, 112.5, 41.1, 34.3, 31.2, 22.1, 21.5; **HRMS** (ESI) calcd for $[C_{21}H_{27}NO_2S + Na]^+$ 380.1660, found 380.1660.

***N*-(2,4-Dimethyl-6-(2-methylallyl)phenyl)-4-methylbenzenesulfonamide 1.93d**

To a stirred solution of **1.92d** (~4.0 mmol, 1.0 equiv) and *p*-toluenesulfonyl chloride (942 mg, 4.9 mmol, 1.2 equiv) in $CH_2Cl_2$ (8.0 mL) at 0 °C was added pyridine (0.65 mL, 8.0 mmol, 2.0 equiv). The reaction was allowed to warm to room temperature over 18 h. The reaction mixture was diluted with $H_2O$ (30 mL) and extracted with $CH_2Cl_2$ (2 x 30 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The resulting mixture was purified by flash column chromatography (1:9 acetone/hexanes) to give sulfonamide **1.93d** as a white powder (864 mg, 2.6 mmol, 65% yield over two steps). $R_f$ = 0.18 (1:9 acetone/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.2 Hz, 2H), 7.27–7.25 (m, 2H), 6.92 (s, 1H), 6.75 (s, 1H), 6.06 (s, 1H), 4.77 (s, 1H), 4.43 (s, 1H), 2.80 (s, 2H), 2.43 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H), 1.54 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.4, 143.6, 138.3, 137.9, 137.5, 137.2, 130.6, 130.59, 129.6, 129.3, 127.1, 111.8, 40.8, 22.4, 21.6, 20.9, 19.1; **HRMS** (ESI) calcd for $[C_{19}H_{23}NO_2S + Na]^+$ 352.1342, found 352.1423.




**1.93b:** $R^1$ = Me, $R^2$ = H
**1.93c:** $R^1$ = *t*Bu, $R^2$ = H
**1.93d:** $R^1$ = Me, $R^2$ = Me

**1.10b:** $R^1$ = Me, $R^2$ = H
**1.10c:** $R^1$ = *t*Bu, $R^2$ = H
**1.10d:** $R^1$ = Me, $R^2$ = Me

***CAUTION!*** *Cyanogen bromide (BrCN) is highly toxic and hydrolyzes readily to release hydrogen cyanide. This preparation must be carried out in a well-ventilated fume hood. Excess BrCN should be destroyed with aqueous NaOH solution, and the resulting aqueous solution should be disposed of properly.*

**Cyanamide 1.10b**[9]

In a fume hood, a stirred solution of **1.93b** (727 mg, 2.3 mmol, 1.0 equiv) in anhydrous $Et_2O$ (9.3 mL) was cooled to 0 °C. Cyanogen bromide (293 mg, 2.8 mmol, 1.2 equiv) was added in one portion followed by dropwise addition of triethylamine (reagent grade, 0.42 mL, 3.0 mmol, 1.3 equiv). The resulting suspension was vigorously stirred at 0 °C for 3 h at which point TLC analysis (1:9 EtOAc/hexanes) indicated the complete consumption of starting material and formation of a lower-running spot (visualized by UV light, followed by $KMnO_4$ stain). The reaction mixture was filtered through a pad of Celite, washed with hexanes, and concentrated *in vacuo*. Flash column chromatography (1:9 EtOAc/hexanes) provided cyanamide **1.10b** (540 mg, 1.6 mmol, 69% yield) as a white powder. $R_f$ = 0.23 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 1.3 Hz, 1H), 6.97 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.66 (d, *J* = 8.1 Hz, 1H), 4.90 (s, 1H), 4.67 (s, 1H), 3.33 (s, 2H), 2.50 (s, 3H), 2.33 (s, 3H), 1.65 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 146.6, 142.7, 141.3, 139.2, 132.9, 131.8, 130.5, 130.2, 128.5, 128.3, 127.7, 113.6, 108.6, 39.2, 22.2, 21.7, 21.2; **IR** (thin film) 2923, 2230, 1650, 1596 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{19}H_{20}N_2O_2S + Na]^+$ 363.1143, found 363.1145.

**Cyanamide 1.10c**

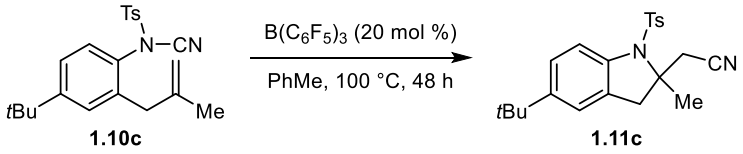
In a fume hood, a stirred solution of **1.93c** (509 mg, 1.4 mmol, 1.0 equiv) in anhydrous $Et_2O$ (5.7 mL) was cooled to 0 °C. Cyanogen bromide (205 mg, 1.9 mmol, 1.4 equiv) was added in one portion followed by dropwise addition of triethylamine (reagent grade, 0.26 mL, 1.9 mmol, 1.3 equiv). The resulting suspension was vigorously stirred at 0 °C for 3 h at which point TLC analysis (1:9 EtOAc/hexanes) indicated the complete consumption of starting material and formation of a lower-running spot (visualized by UV light, followed by $KMnO_4$ stain). The reaction mixture was filtered through a pad of Celite, washed with hexanes, and concentrated *in vacuo*. Flash column chromatography

[9] Procedure was adapted from: Koester, D. C.; Kobayashi, M.; Werz, D. B.; Nakao, Y. *J. Am. Chem. Soc.* **2012**, *134*, 6544.

(1:9 EtOAc/hexanes) provided cyanamide **1.10c** (157 mg, 0.41 mmol, 29% yield) as a white powder. $R_f$ = 0.28 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 4.91 (app s, 1H), 4.66 (app s, 1H), 3.36 (br s, 2H), 2.51 (s, 3H), 1.67 (s, 3H), 1.29 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 154.2, 146.6, 142.8, 138.8, 133.2, 130.5, 130.3, 128.6, 128.5, 127.5, 124.6, 113.5, 108.7, 39.6, 34.8, 31.1, 22.3, 21.8; **IR** (thin film) 2965, 2229, 1652, 1595 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{22}H_{28}N_2O_2S + Na]^+$ 405.1613, found 405.1614.

**Cyanamide 1.10d**

In a fume hood, to a stirred solution of **1.93d** (830 mg, 2.5 mmol, 1.0 equiv) in anhydrous MeCN (5.1 mL) was added cyanogen bromide (347 mg, 3.3 mmol, 1.3 equiv) in one portion followed potassium carbonate (697 mg, 5.0 mmol, 2.0 equiv). The resulting suspension was vigorously stirred at room temperature for 29 h at which point TLC analysis (1:9 EtOAc/hexanes) indicated complete consumption of starting material and formation of a higher-running spot (visualized by UV light, followed by $KMnO_4$ stain). The reaction mixture was diluted with $H_2O$ and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated. Precipitation from $Et_2O$/heptane provided cyanamide **1.10d** (406 mg, 1.1 mmol, 45% yield) as a white powder. $R_f$ = 0.32 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, CDCl3) δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 4.87 (s, 1H), 4.59 (s, 1H), 3.33 (d, *J* = 15.8 Hz, 1H), 3.03 (d, *J* = 15.7 Hz, 1H), 2.50 (s, 3H), 2.30 (s, 3H), 2.00 (s, 3H), 1.60 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 146.6, 143.0, 140.8, 139.7, 137.6, 134.3, 130.6, 130.4, 129.5, 129.4, 128.4, 113.4, 108.3, 39.9, 22.2, 21.8, 21.1, 17.9; **IR** (thin film) 2924, 2223, 1651, 1596 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{20}H_{22}N_2O_2S + Na]^+$ 377.1294, found 377.1298.




**2-(2,5-Dimethyl-1-tosylindolin-2-yl)acetonitrile 1.11b**

In a nitrogen-filled glove box, a 1-dram vial was charged with a magnetic stirring bar, cyanamide **1.10b** (34.0 mg, 0.10 mmol, 1.0 equiv), tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol, 1.0 equiv) and toluene (0.5 mL). The resulting mixture was sealed with a PTFE-lined cap, removed from the glove box, and heated at 90 °C in an aluminum heating block for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (2.0 mL). TLC analysis (1:4 EtOAc/hexanes) indicated the complete consumption of starting material and formation of a lower-running spot (visualized by UV light). The resulting solution was concentrated onto Celite and purified by flash column chromatography (1:4 EtOAc/hexanes) to give indoline **1.11b** as a viscous light yellow oil (31.3 mg, 0.092 mmol, 92% yield). $R_f$ = 0.28 (1:4 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) δ 7.82 (dt, *J* = 8.7, 2.1 Hz, 2H); 7.30 (dd, *J* = 8.7, 0.6 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 1H), 6.99 – 6.96 (m, 2H), 3.32 (d, *J* = 16.3 Hz, 1H), 3.22 (d, *J* = 16.7 Hz, 1H), 3.08 (d, *J* = 16.7 Hz, 1H), 3.03 (d, *J* = 16.3 Hz, 1H), 2.39 (s, 3H), 2.27 (s, 3H), 1.71 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.1, 139.0, 138.2, 133.2, 129.8, 128.6, 126.8, 126.7, 125.8, 117.2, 113.9, 68.9, 43.4, 29.9, 25.2, 21.5, 20.7; **IR** (thin film) 2978, 2253, 2598, 1488 $cm^{-1}$; **HRMS** (ESI) calc for $[C_{19}H_{20}N_2O_2S + Na]^+$ 363.1143, found 363.1140.

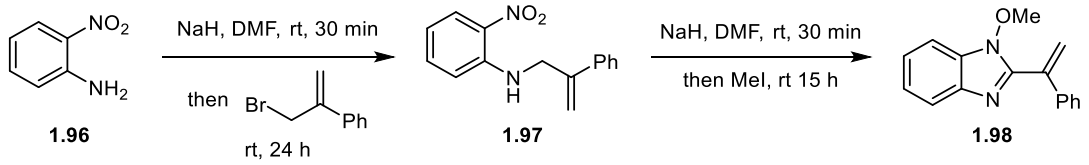
**2-(5-(*tert*-butyl)-2-methyl-1-tosylindolin-2-yl)acetonitrile 1.11c**

In a nitrogen-filled glovebox, a 1-dram vial was charged with a magnetic stirring bar, cyanamide **1.10c** (38.1 mg, 0.10 mmol, 1.0 equiv), tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol, 1.0 equiv) and toluene (0.5 mL). The resulting mixture was sealed with a PTFE-lined cap, removed from the glove box, and heated at 90 °C in an aluminum heating block for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (2.0 mL). The TLC analysis (1:4 EtOAc/hexanes) indicated the complete consumption of starting material and formation of a lower-running spot (visualized by

UV light). The resulting solution was concentrated onto Celite and purified by flash column chromatography (1:4 EtOAc/hexanes) to give indoline **1.11c** as a white solid (33.6 mg, 0.094 mmol, 94% yield). A second reaction with **1.10c** (38.3 mg, 0.10 mmol) gave **1.11c** (33.6 mg, 0.087 mmol, 88% yield) after chromatography. $R_f$ = 0.33 (1:4 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.24 (s, 1H), 7.17 – 7.16 (m, 2H), 3.38 (d, *J* = 16.1 Hz, 1H), 3.24 (d, *J* = 16.6 Hz, 1H), 3.19 (d, *J* = 16.6 Hz, 1H), 3.05 (d, *J* = 16.1 Hz, 1H), 2.40 (s, 3H), 1.78 (s, 3H), 1.27 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 146.6, 144.1, 138.8, 138.2, 129.8, 126.9, 126.2, 125.1, 122.2, 117.3, 133.4, 69.1, 43.6, 34.3, 31.4, 29.8, 25.3, 21.6; **IR** (thin film) 2963, 2254, 1598, 1492 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{22}H_{26}N_2O_2S + Na]^+$ 405.1613, found 405.1619.

**2-(2,5,7-Trimethyl-1-tosylindolin-2-yl)acetonitrile 1.11d**

In a nitrogen-filled glovebox, a 1-dram vial was charged with a magnetic stirring bar, cyanamide **1.10d** (35.4 mg, 0.10 mmol, 1.0 equiv), tris(pentafluorophenyl)borane (51.2 mg, 0.10 mmol, 1.0 equiv) and toluene (0.5 mL). The resulting mixture was sealed with a PTFE-lined cap, removed from the glove box, and heated at 90 °C in an aluminum heating block for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (1.0 mL). The TLC analysis (1:4 EtOAc/hexanes) indicated the complete consumption of starting material and formation of a lower-running spot (visualized by UV light). The resulting solution was concentrated onto Celite and purified by flash column chromatography (1:4 EtOAc/hexanes) to give indoline **1.11d** as a white solid (31.8 mg, 0.090 mmol, 90% yield). $R_f$ = 0.30 (1:4 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.27 Hz, 2H), 7.19 (d, *J* = 8.14 Hz, 2H), 6.97 (s, 1H), 6.81 (s, 1H), 2.62 (d, *J* = 16.7 Hz, 1H), 2.51 (d, *J* = 15.9 Hz, 1H), 2.49 (s, 3H), 2.44–2.40 (m, 2H), 2.40 (s, 3H), 2.32 (s, 3H), 1.75 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 144.1, 139.2, 137.2, 137.1, 135.9, 134.0, 131.4, 129.5, 127.6, 123.2, 116.8, 69.3, 41.2, 30.0, 22.3, 21.6, 21.1, 19.9; **IR** (thin film) 2926, 2254, 1598, 1472 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{20}H_{22}N_2O_2S + Na]^+$ 377.1294, found 377.1334.




α-Bromomethylstyrene was prepared from α-methylstyrene following a known procedure.[10]

**2-Nitro-*N*-(2-phenylallyl)aniline 1.97**

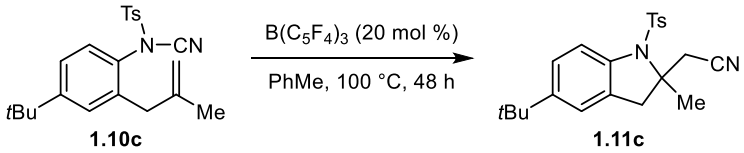
To 2-nitroaniline (833 mg, 6.0 mmol, 1.0 equiv) in DMF (15.0 mL) at room temperature was added sodium hydride (278 mg, 6.6 mmol, 1.1 equiv). The reaction mixture was allowed to stir at room temperature for 30 min then α-bromomethylstyrene (1.43 g, 7.3 mmol, 1.2 equiv) was added dropwise, and the reaction mixture was allowed to stir at room temperature for 24 h. The reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:9 EtOAc/hexanes) provided amine **1.97** as a bright orange solid (846 mg, 3.3 mmol, 55% yield). $R_f$ = 0.36 (1:9 EtOAc/hexane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.33 (br s, 1H), 8.19 (dd, *J* = 8.6, 1.6), 7.46–7.32 (m, 6H), 6.84 (dd, *J* = 8.5, 0.5), 6.68 (ddd, *J* = 8.5, 7.1, 1.3, 1H), 5.52 (d, *J* = 0.39, 1H), 5.30 (app s, 1H), 4.37 (d, *J* = 5.8, 2H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 145.2, 142.8, 138.7, 136.2, 132.1, 128.6, 128.2, 126.8, 126.0, 115.7, 114.1, 113.7, 46.8; **IR** (thin film) 3391, 1618, 1575, 1513, 1442, 1353 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{15}H_{14}N_2O_2 + Na]^+$ 277.0947, found 277.0982.

**1-Methoxy-2-phenyl-1*H*-benzo[*d*]imidazole 1.98**

To sodium hydride (150 mg, 3.7 mmol, 1.1 equiv) in DMF (4.8 mL) at room temperature was added **1.97** (846 mg, 3.3 mmol, 1.0 equiv) in DMF (4.8 mL) dropwise. The reaction mixture was allowed to stir at room temperature for 30 min, during which evolution of gas was observed. Methyl iodide (0.23 mL, 3.7 mmol, 1.1 equiv) in DMF (1.6 mL) was

[10] Martin, D. B. C.; Nguyen, L. Q.; Vanderwal, C. D. *J. Org. Chem.* **2012**, *77*, 17.

added, and the reaction mixture was allowed to stir at room temperature for 15 h. The reaction was quenched was quenched with saturated aqueous $NH_4Cl$ (20 mL) and extracted with $Et_2O$ (3 x 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (1:9 EtOAc/hexanes) provided benzimidazole **1.98** (380 mg, 1.7 mmol, 46% yield). $R_f$ = 0.45 (1:9 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.8, 1H), 7.47–7.45 (m, 3H), 7.40–7.36 (m, 3H), 7.34 (dt, *J* = 7.0, 1.0, 1H), 7.30 (dt, *J* = 1.5, 8.0, 1H), 6.15 (s, 1H), 6.00 (s, 1H), 3.86 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 147.7, 138.3, 138.2, 138.0, 130.6, 128.35, 128.3, 127.3, 123.6, 122.7, 121.8, 120.6, 108.4, 65.3; **IR** (thin film) 3057, 2937, 1490, 1443, 1318; **HRMS** (ESI) calcd for $[C_{16}H_{15}N_2O + H]^+$ 251.1179, found 251.1169. The structure was confirmed by HSQC, and HMBC.

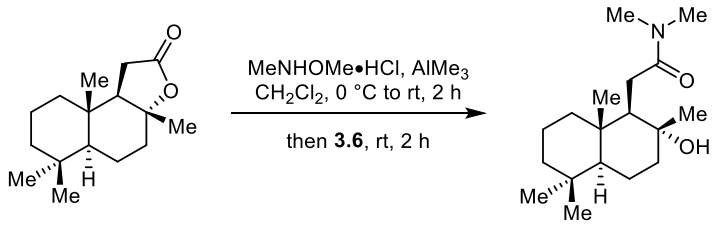



**1.10c** **1.11c**

**Large-scale, catalytic aminocyanation in air**

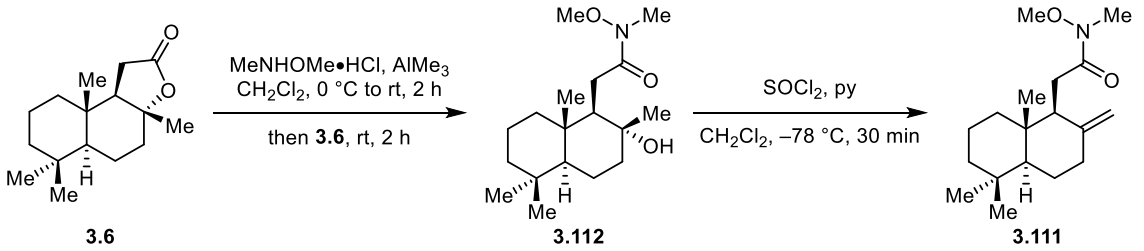
On the benchtop, a 1-dram vial was charged with a magnetic stirring bar, cyanamide **1.10c** (765 mg, 2.0 mmol, 1.0 equiv), tris(pentafluorophenyl)borane (205 mg, 0.4 equiv, 20 mol %), and toluene (8.0 mL). The resulting mixture was sealed with a PTFE-lined cap, removed from the glove box, and heated at 100 °C for 48 h in an aluminum heating block for 24 h. The reaction mixture was cooled to room temperature and diluted with EtOAc (40 mL). The resulting solution was concentrated onto Celite and purified by flash column chromatography (1:4 EtOAc/hexanes) to give indoline **1.11c** as a white solid (720 mg, 1.9 mmol, 94% yield). The $^1$H NMR spectroscopic data of **1.11c** was consistent with the data previously described.

**Experimental Section for Part II**

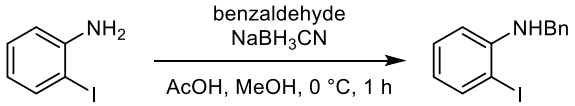



***N,N*-dimethylacetamide 3.113**

A solution of MeNHOMe•HCl (0.16 g, 1.6 mmol, 2.0 equiv) in $CH_2Cl_2$ (1.6 mL) was stirred at 0 °C. $Me_3Al$ (2.0 M in toluene, 1.20 mL, 2.4 mmol, 3.0 equiv) was added dropwise over 4 min. The reaction mixture was warmed to rt and stirred for 2 h. (+)-Sclareolide (0.20 g, 0.81 mmol, 1.0 equiv) was added to the reaction mixture, and the mixture was allowed to stir at rt for 2 h. The reaction mixture was cooled to 0 °C, and 10% (v/v) $H_2SO_4$ (1.2 mL) was added dropwise. The mixture was allowed to warm to rt then washed with water (1 x 5 mL). The aqueous portion was extracted with $CH_2Cl_2$ (2 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (100% Hex then 3:7 EtOAc:Hex) provided **3.113** as white needle-like crystals (0.14 g, 0.44 mmol, 57% yield): $R_f$ = 0.16 (3:7 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.29 (s, 1H), 3.08 (s, 3H), 2.96 (s, 3H), 2.41 (dd, *J* = 16.7, 2.9 Hz, 1H), 2.31 (dd, *J* = 16.6, 6.8 Hz, 1H), 2.07 – 2.01 (m, 1H), 1.95 (dt, *J* = 12.6, 3.2 Hz, 1H), 1.73 – 1.66 (m, 1H), 1.58 (tt, *J* = 13.4, 3.5 Hz, 1H), 1.54 – 1.47 (m, 1H), 1.47 – 1.39 (m, 1H), 1.39 – 1.33 (m, 1H), 1.29 – 1.24 (m, 1H), 1.19 – 1.11 (m, 1H), 1.16 (3H, s), 1.04 (dd, *J* = 12.3, 2.4 Hz, 1H), 0.98 (td, *J* = 12.7, 3.7 Hz, 1H), 0.88 (s, 3H), 0.82 (s, 3H), 0.79 (s, 3H); **$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 175.6, 73.4, 56.9, 56.6, 45.2, 42.4, 40.1, 40.0, 39.8, 39.3, 38.1, 36.8, 34.1, 34.0, 29.1, 24.0, 22.1, 21.3, 19.2, 16.7; **IR** (thin film) 3197, 2998, 1618, 1386 cm$^{-1}$; **HRMS** (ESI) calcd for $[2(C_{18}H_{33}NO_2) + Na]^+$ 613.4920, found 613.4929; $[\alpha]_{589}^{22.7}$ = +37 (c = 0.0063 g mL$^{-1}$, $CH_2Cl_2$).




Weinreb amide **3.112** was prepared from (+)-sclareolide **3.6** according to Boukouvalas et al.[11] Olefin **3.111** was prepared from **3.112** according to Boukouvalas et al;[11] the procedure was modified as described in the text. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.73 (s, 1H), 4.44 (s, 1H), 3.72 (s, 3H), 3.16 (s, 3H), 2.69 (dd, *J* = 15.6, 10.2 Hz, 1H), 2.50 (d, *J* = 10.3 Hz, 1H), 2.39 (dq, *J* = 12.2, 4.5 Hz, 2H), 2.14 (td, *J* = 12.9, 5.2 Hz, 1H), 1.73 (dt, *J* = 12.6, 2.6 Hz, 1H), 1.59–1.45 (m, 4H), 1.41–1.36 (m, 1H), 1.32 (td, *J* = 12.7, 4.2 Hz, 1H), 1.26–1.13 (m, 3H), 0.88 (s, 3H), 0.82 (s, 3H), 0.74 (s, 3H). The $^1$H NMR spectroscopic data of **3.111** are in excellent agreement with those reported in the literature.[11]




**_N_-Benzyl-2-iodoaniline 3.116**

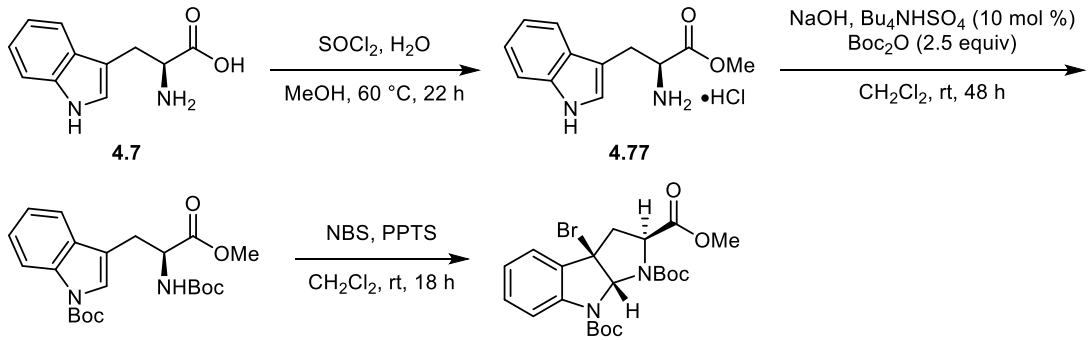
To 2-iodoaniline (2.00 g, 9.1 mmol, 1.0 equiv) in MeOH (22.8 mL) at rt were added benzaldehyde (0.93 mL, 9.1 mmol, 1.0 equiv) and acetic acid (1.31 mL, 22.8 mmol, 2.5 equiv). The reaction mixture was cooled to 0 °C, and $NaBH_3CN$ (0.86 g, 13.7 mmol, 1.5 equiv) was added. The reaction mixture was stirred at 0 °C for 40 min then concentrated *in vacuo* to remove the MeOH. The product mixture was dissolved in EtOAc and extracted with saturated aqueous $NaHCO_3$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (100% hexanes to 1:99 EtOAc/hexanes over 20 min) provided *N*-benzyl-2-iodoaniline as a brown oil (1.94 g, 6.3 mmol, 69% yield). $R_f$ = 0.45 (2:98

[11] Boukouvalas, J.; Wang, J.-X.; Marion, O.; Ndzi, B. *J. Org. Chem.* **2006**, *71*, 6670.

EtOAc/hexanes); **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.38 (app s, 2H), 7.36 (app s, 2H), 7.33–7.27 (m, 1H), 7.16 (ddd, *J* = 8.1, 7.3, 1.4 Hz, 1H), 6.54 (dd, *J* = 8.2, 1.4 Hz, 1H), 6.46 (td, *J* = 7.5, 1.5 Hz, 1H), 4.64–4.62 (br s, 1H), 4.41 (d, *J* = 5.6 Hz, 2H). The $^1$H NMR spectroscopic data of **3.116** are in excellent agreement with those reported in the literature.[12]


**3.115** **3.122** **3.123**

*N*-Boc-2-iodoaniline **3.122** was prepared from 2-iodoaniline according to Akita et al.[13] **3.122** was obtained as an inseparable mixture with **3.123**.



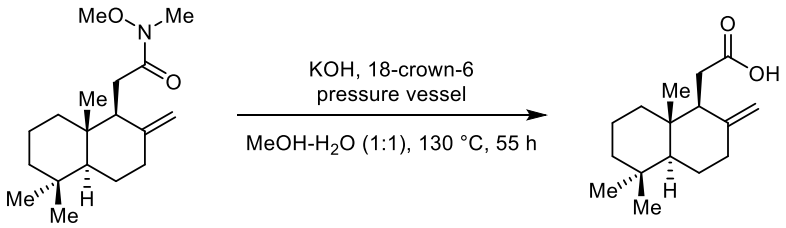

**4.7** **4.77** **4.51** **4.5**

L-Tryptophan methyl ester hydrochloride **4.77** was prepared from L-tryptophan according to Makinen et al.[14] *N,N′*-bis(Boc)-L-tryptophan methyl ester **4.51** was prepared from **4.77** according to Danishefsky et al.[15] Bromopyrroloindoline **4.5** was prepared from **4.51** according to Rainier et al.[16] Cyclic voltammetry in THF using a Ag/AgCl reference electrode provided a first reduction potential of –0.800 eV.[17] **$^1$H NMR** (500 MHz,

---

[12] Cropper, E. L.; White, A. J. P.; Ford, A.; Hii, K. K. (M.) *J. Org. Chem.* **2006**, *71*, 1732.
[13] Sutou, N.; Kato, K.; Akita, H. *Tetrahedron: Asymmetr.* **2008**, *19*, 1833.
[14] Wells, G. B.; Mustafi, D.; Makinen, M. W. *J. Am. Chem. Soc.* **1990**, *112*, 2566.
[15] Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953.
[16] Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894.
[17] Cyclic voltammetry performed by Lafe Purvis.

$CD_2Cl_2$) δ 7.47 (br s, 1H), 7.31 (dt, *J* = 7.7, 0.6 Hz, 1H), 7.27–7.24 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.26 (s, 1H), 3.79 (dd, *J* = 10.1, 6.5 Hz, 1 H), 3.64 (s, 3H), 3.19–3.15 (m, 1H), 2.72 (dd, *J* = 12.7, 10.2 Hz, 1 H), 1.50 (s, 9H), 1.29 (s, 9H); $[\alpha]_{589}^{22.7}$ = –165 (c = 0.010 g $mL^{-1}$, $CH_2Cl_2$). $^1H$ NMR spectroscopic data and optical rotation of **4.5** are in excellent agreement with those reported in the literature.[16]

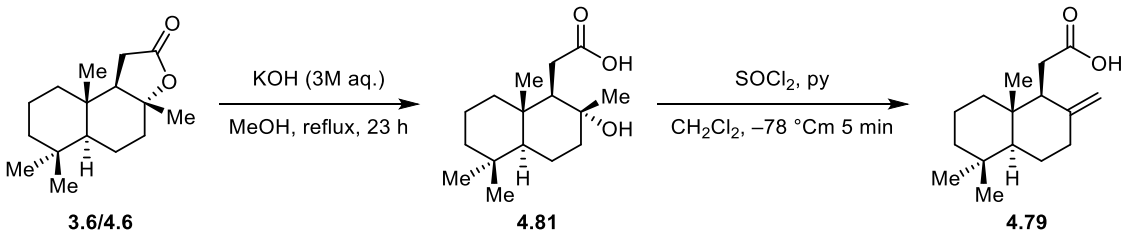



**3.111/4.78** **4.79**

**Δ$^{8,13}$-bicyclohomofarnezenic acid 4.79**

A pressure vessel was charged with Weinreb amide **4.78** (310 mg, 1.0 mmol, 1.0 equiv), freshly crushed potassium hydroxide (600 mg, 10.7 mmol, 10 equiv), 18-crown-6 (220 mg, 0.8 mmol, 0.8 equiv), deionized $H_2O$ (1.50 mL), and methanol (1.50 mL). The pressure vessel was sealed and heated at 130 °C in an oil bath for 55 h. The reaction mixture was cooled to rt, diluted with $H_2O$ and $CH_2Cl_2$, and acidified with aqueous HCl (2M, pH = 2). The aqueous phase was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (3:2 EtOAc/hexanes) provided **4.79** as a white solid (127 mg, 0.5 mmol, 50% yield). $R_f$ = 0.9 (3:2 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.54 (s, 1H), 2.53 (dd, *J* = 16.0, 3.6 Hz, 1H), 2.46–2.37 (m, 2H), 2.36–2.30 (m, 1H), 2.10 (tt, *J* = 13.2, 5.3 Hz, 1H), 1.74 (ddt, *J* = 12.9, 5.2, 2.5 Hz, 1H), 1.63–1.54 (m, 2H), 1.54–1.45 (m, 1H), 1.44–1.38 (m, 1H), 1.36 (dd, *J* = 12.9, 4.3 Hz, 1H), 1.31 (dd, *J* = 12.9, 4.3 Hz, 1H), 1.28–1.24 (m, 1H), 1.13 (dd, *J* = 12.2, 4.7 Hz, 1H), 0.89 (s, 3H), 0.82 (s, 3H), 0.70 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 173.5, 149.4, 106.5, 55.1, 53.4, 52.4, 42.0, 38.9, 37.7, 33.6, 32.4, 29.7, 24.1, 21.7, 19.3, 14.6; **IR** (thin film) 2926, 2866, 2843, 1705, 1645 $cm^{-1}$; **LRMS** (CI, MeOH) *m/z* 250 $(M + 1)^+$, 235 (M

– $CH_3)^+$; $[\alpha]_{589}^{23.3}$ = –62 (c = 0.0014 g $mL^{-1}$, $CH_2Cl_2$).

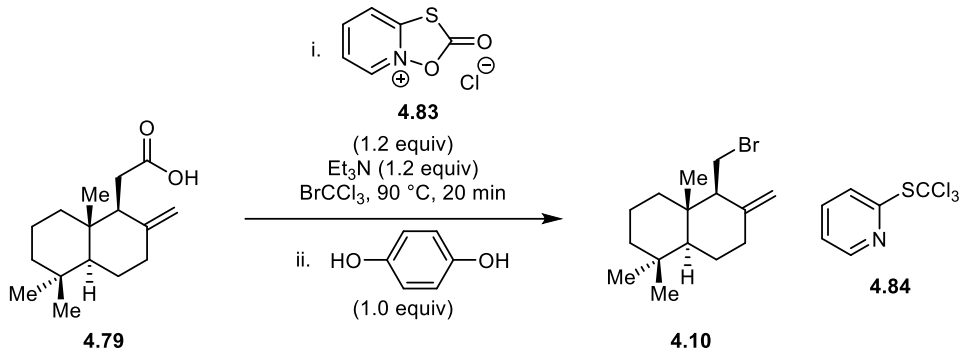



Carboxylic acid **4.81** was prepared from (+)-sclareolide according to Yabuuchi and Kusumi.[18]

**$\Delta^{8,13}$-bicyclohomofarnezenic acid 4.79**

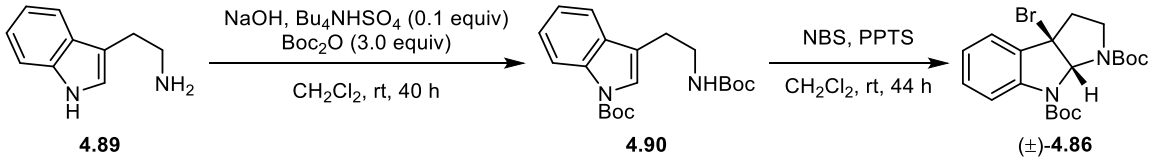
To a flask equipped with an internal temperature monitor was added **4.81** (500 mg, 1.9 mmol, 1.0 equiv) and $CH_2Cl_2$ (11.6 mL). The reaction mixture was cooled to an internal temperature of –74 °C, and pyridine was added (0.30 mL, 2.0 equiv). The reaction mixture was allowed to cool to an internal temperature of –74 °C, and a solution of pyridine (1.24 mL, 8.3 mmol) and $SOCl_2$ (0.67 mL, 5.0 equiv) in $CH_2Cl_2$ (5.80 mL) was added dropwise over 15 min. The internal temperature varied from –74 °C to –70 °C during the addition. The reaction mixture was allowed to stir at –74 °C for 5 min then quenched with saturated $NaHCO_3$ in MeOH (25 mL). The reaction mixture was allowed to warm to room temperature and was diluted with $H_2O$ and $CH_2Cl_2$. The organic extract was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (3:2 EtOAc/hexanes) provided **4.79** as a white solid (68 mg, 0.3 mmol, 15%). The $^1$H NMR spectroscopic data of **4.79** was consistent with the data previously described.

[18] Yabuuchi, T.; Kusumi, T. *J. Org. Chem.* **2000**, *65*, 397.




**Bromide 4.10**

A suspension of 1-oxa-2-oxo-3-thiaindolizinium chloride **4.83** (112 mg, 0.59 mmol, 1.2 equiv) and $Et_3N$ (85 μL, 1.2 equiv) in $BrCCl_3$ (4.2 mL) was prepared and warmed to 90 °C. A solution of carboxylic acid **4.79** (123 mg, 0.49 mmol, 1.0 equiv) in $BrCCl_3$ (2.45 mL) was added to the stirred suspension dropwise over 5 min. The reaction mixture was allowed to stir at 90 °C for 20 min. The reaction mixture was cooled to rt, poured over hydroquinone (54 mg, 0.49 mmol, 1.0 equiv), diluted with pentane, and washed with aqueous HCl (0.1 M, 3 x 10 mL). The organic extract was dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (100% pentane then 100% $CH_2Cl_2$) provided **4.10** as a yellow oil (59.6 mg, 0.21 mmol, 43%). $R_f$ = 0.40 (100% pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 5.02 (s, 1H), 4.71 (s, 1H), 3.79 (m, 1H), 3.40 (t, *J* = 10.5 Hz, 1H), 2.47 (dt, *J* = 13.2, 3.0 Hz, 1H), 2.27–0.92 (m, 11H), 0.91 (s, 3H), 0.83 (s, 3H), 0.83 (s, 3H), 0.74 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 145.5, 107.9, 59.5, 55.1, 52.8, 41.9, 41.1, 39.1, 37.6, 33.6, 29.8, 24.1, 21.7, 19.2, 14.5; IR (thin film) 2928, 2868, 1459, 1264 cm$^{-1}$; LRMS (CI, MeOH) *m/z* 285 $(M + 1)^+$, 205.6 $(M - Br)^+$; $[\alpha]_{589}^{23.6}$ = +29 (c = 0.0055 g mL$^{-1}$, $CH_2Cl_2$).



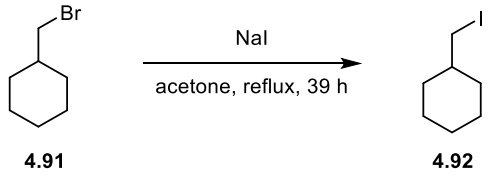

**4.89** **4.90** (±)-**4.86**

***N,N′*-bis(*tert*-butyloxycarbonyl)-tryptamine (4.90)**

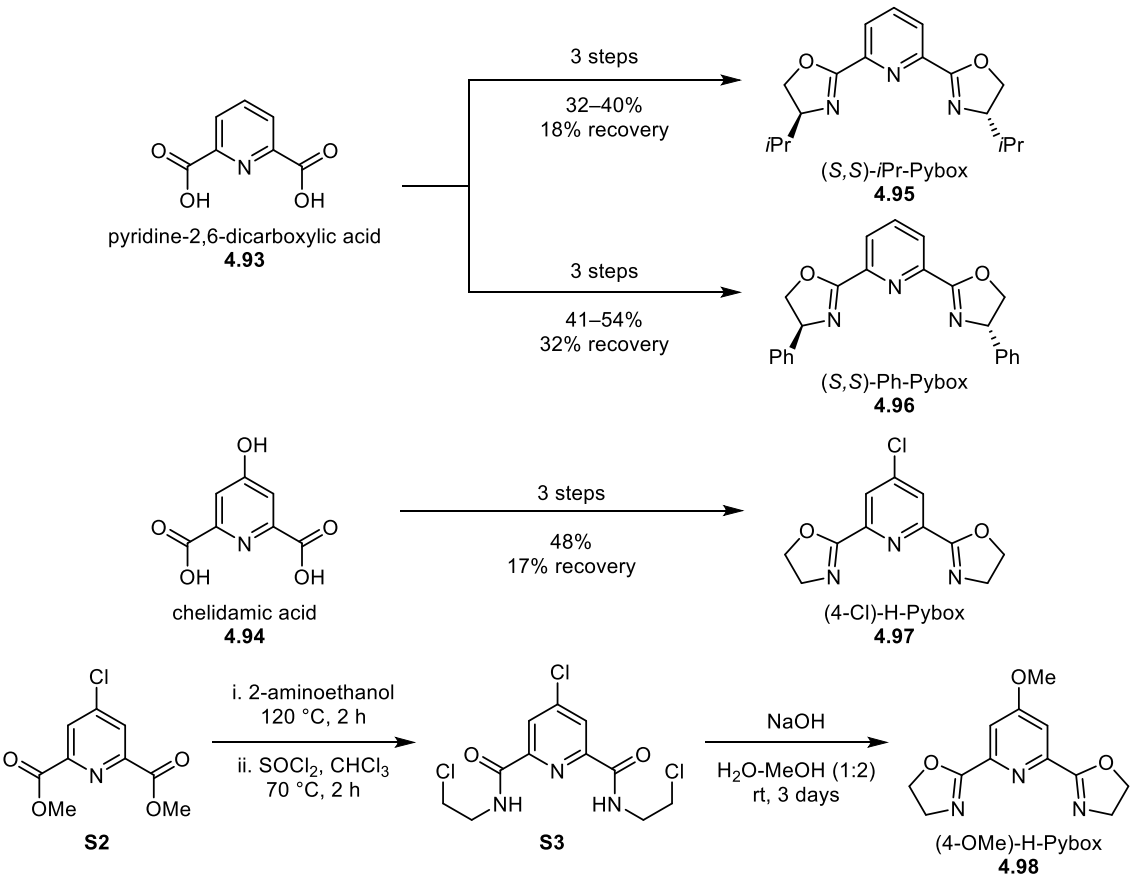
To a solution of tryptamine (2.00 g, 12.5 mmol, 1.0 equiv) and $Bu_4NHSO_4$ (424 mg, 1.3 mmol, 0.10 equiv) in $CH_2Cl_2$ (130.0 mL) at rt was added freshly ground NaOH (2.61 g, 65.3 mmol, 5.2 equiv). The reaction mixture was allowed to stir at rt for 3 h. $Boc_2O$ (8.17 g, 37.4 mmol, 3.0 equiv) was added in one portion, and the reaction mixture was allowed to stir at rt for 40 h. The reaction mixture was filtered through Celite and concentrated *in vacuo*. Purification by flash column chromatography (1:3 EtOAc/hexanes) provided **4.90** as a thick yellow oil (4.01 g, 11.1 mmol, 89%). $R_f$ = 0.38 (1:3 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.41 (s, 1H), 7.32 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.25–7.22 (m, 1H), 4.64 (s, 1H), 3.46 (q, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 6.8 Hz, 2H), 1.67 (s, 9H), 1.44 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 155.9, 149.7, 135.1, 130.4, 124.4, 123.1, 122.4, 118.9, 117.7, 115.2, 83.5, 79.2, 40.2, 28.4, 28.2, 25.5; **IR** (thin film) 3451, 2981, 2934, 1811, 1708 cm$^{-1}$; **HRMS** (ESI) calcd for $[C_{20}H_{28}N_2O_4 + K]^+$ 399.1681, found 399.2149. $^1$H NMR spectroscopic data of **4.90** are in excellent agreement with those reported in the literature.[19]

Bromopyrroloindoline **4.86** was prepared from **4.90** according to Espejo and Rainier.[20]

[19] Xie, W.; Jiang, G.; Liu, H.; Hu, J.; Pan, X.; Zhang, H.; Wan, X.; Lai, Y.; Ma, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 12924.
[20] Espejo, V. R.; Rainier, J. D. *J. Am. Chem. Soc.* **2008**, *130*, 12894.




(Iodomethyl)cyclohexane **4.92** was prepared from (bromomethyl)cyclohexane by the Finkelstein reaction according to Cammidge and Cook.[21]



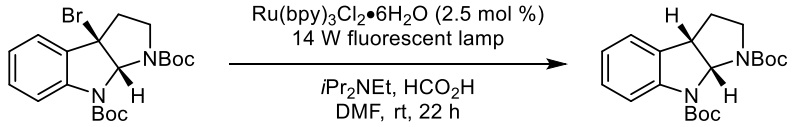

(*S*,*S*)-*i*Pr-Pybox **4.95** and (*S*,*S*)-Ph-Pybox **4.96** were prepared from pyridine-2,6-dicarboxylic acid **4.93** in three steps following Nishiyama et al.[22] (4-Cl)-H-Pybox **4.97** was prepared from chelidamic acid **4.94** in three steps. The first step, preparation of

[21] Cammidge, A. N.; Tseng, C.-H.; Chambrier, I.; Hughes, D. L.; Cook, M. J. *Tetrahedron Lett.* **2009**, *50*, 5254.
[22] Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.

dimethyl 4-chloropyridine-2,6-dicarboxylate **S2**, was conducted according to Desreux et al.[23] for the procedure and Chessa et al.[24] for the workup. The second step (preparation of **S3**) and third step were conducted according to Marcelis et al.[25]

**(4-OMe)-H-Pybox 4.98**

To crude **S3** (~118 mg, 0.36 mmol, 1.0 equiv) in MeOH (2.40 mL) and $H_2O$ (1.20 mL) at rt was added freshly ground NaOH (199 mg, 5.0 mmol, 14 equiv) in one portion. The reaction mixture was allowed to stir at rt for 3 days then concentrated *in vacuo* to remove the MeOH and extracted with $CH_2Cl_2$. The organic phase was back-extracted with $H_2O$, washed with brine, and concentrated. The product was recrystallized twice: once from $CH_2Cl_2$/pentane and once from EtOAc to provide **4.98** as white crystals (13.9 mg, 0.06 mmol, 16% yield). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.69 (s, 2H), 4.53 (t, *J* = 9.7 Hz, 4H), 4.11 (t, *J* = 9.7 Hz, 4H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 166.6, 163.5, 148.2, 111.6, 68.3, 55.8, 54.9; **IR** (thin film) 1647, 1591, 1567, 1465, 1402, 1219, 1091, 982 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{12}H_{13}N_3O_3 + Na]^+$ 270.0849, found 270.0902. $^1$H NMR spectroscopic data of **4.98** are in excellent agreement with those reported in the literature.[26]




(±)-**4.86** (±)-**4.99**

Tetrahydropyrrolo[2,3-*b*]indole (±)-**4.99** was prepared from bromopyrroloindoline (±)-**4.86** according to Stephenson et al.[27]

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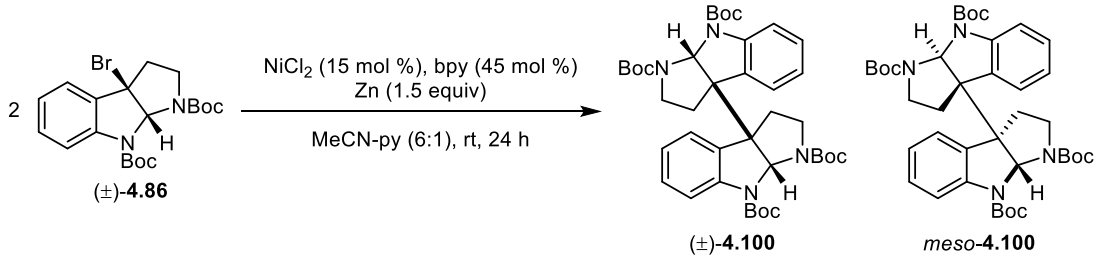
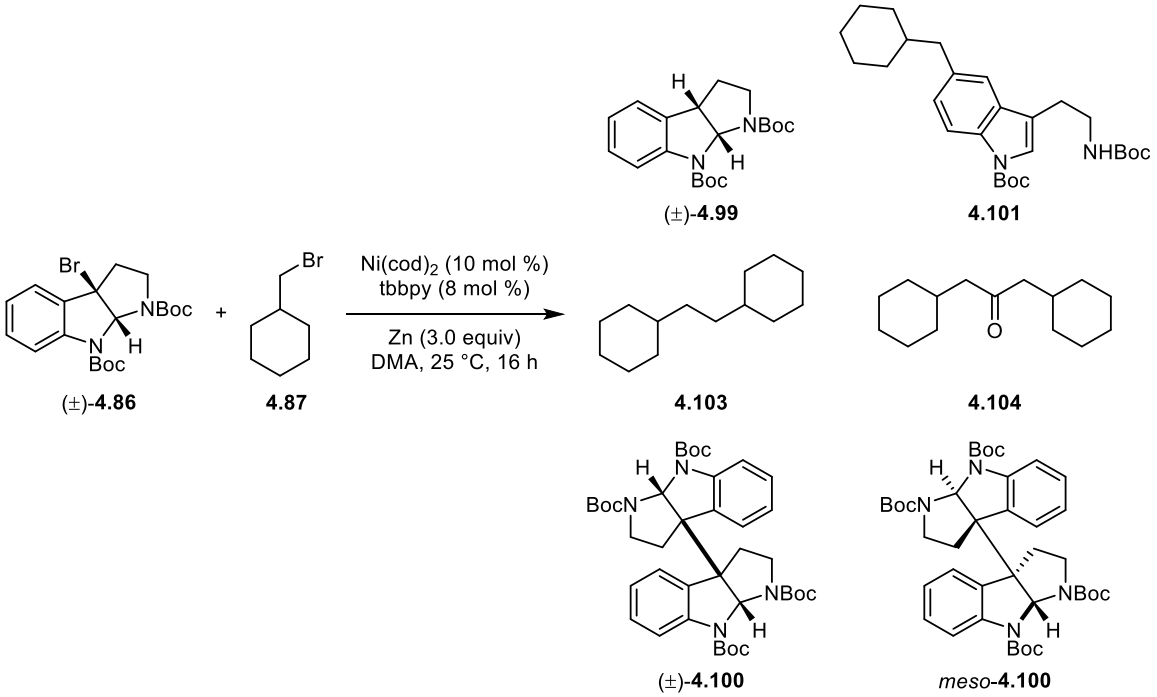
[23] Dumont, A.; Jacques, V.; Desreux, J. F. *Tetrahedron* **2000**, *56*, 2043.
[24] Chessa, G.; Canovese, L.; Visentin, F.; Santo, C.; Seraglia, R. *Tetrahedron* **2005**, *61*, 1755.
[25] Vermonden, T.; Branowska, D.; Marcelis, A. T. M.; Sudhölter, E. J. R. *Tetrahedron* **2003**, *59*, 5039.
[26] de Bettencourt-Dias, A.; Barber, P. S.; Viswanathan, S.; de Lill, D. T.; Rollett, A.; Ling, G.; Altun, S. *Inorg. Chem.* **2010**, *49*, 8848.
[27] Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.




**Homodimers (±)- and *meso*-4.100**

Zinc powder was activated with aqueous HCl (1M) then filtered, rinsing with $H_2O$, MeOH, and $Et_2O$. To a 10-mL flask was added $NiCl_2$ (7.6 mg, 0.06 mmol, 30 mol %) and activated zinc powder (22.5 mg, 0.34 mmol, 1.7 equiv). The flask was purged with $N_2$, and pyridine (0.15 mL) and bipy (15.0 mg, 0.10 mmol, 50 mol %) were added. The reaction mixture was heated at 55 °C for 10 minutes then cooled to rt. A solution of (±)-**4.86** (88.6 mg, 0.20 mmol, 1.0 equiv) in MeCN (1.0 mL) was added, and the reaction mixture was allowed to stir at rt for 24 h. The reaction mixture was filtered through a plug of silica gel, washing with EtOAc (15.0 mL). The product mixture was extracted with $H_2O$ (3 x 10 mL), washed with brine (3 x 10 mL), dried over $Na_2SO_4$, filtered, and concentrated. Purification by column chromatography (1:4 acetone/pentane, basified with 1% v/v $Et_3N$) provided (±)-**4.100** and *meso*-**4.100** as a mixture in 31% yield. $R_f$ = 0.4 (1:4 acetone/pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.13 (br s, 2H), 7.54 (d, *J* = 7.7 Hz, 2H), 7.41 (d, *J* = 0.2 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.24 (t, *J* = 7.5 Hz, 2H), 3.47–3.44 (m, 4H), 2.90 (dd, *J* = 9.0, 4.5 Hz, 4H), 1.67 (s, 18H), 1.44 (s, 18H); **IR** (thin film) 2972, 2932, 2884, 1467, 1380, 1162, 1130 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{40}H_{54}N_4O_8 + Na]^+$ 741.3834, found 741.4114.




**Nickel-catalyzed reductive cross coupling of (±)-4.86 and 4.87**

Bromopyrroloindoline (±)-**4.86** (1.76 g, 4.0 mmol, 1.0 equiv), (bromomethyl)cyclohexane (1.67 mL, 12.0 mmol, 3.0 equiv), $Ni(cod)_2$ (110 mg, 0.40 mmol, 10 mol %), tbbpy (86 mg, 0.32 mmol, 8 mol %), zinc powder (785 mg, 12.0 mmol, 3.0 equiv), and 16.0 mL DMA were divided equally into eight 1-dram vials. The vials were sealed with PTFE-lined caps and were allowed to stir at 25 °C for 16 h in an aluminum block heater. The reaction mixtures were combined and filtered through a plug of Celite, washing with EtOAc/hexanes (1:9). The product mixture was concentrated *in vacuo*. Flash column chromatography (1:3 EtOAc/hexanes) provided four fractions: **A**, **B**, **C**, and **D**. Fractions **C** and **D** contained mixtures of (±)-**4.99**, (±)-**4.100**, and *meso*-**4.100**.

Fraction **A** was purified by flash column chromatography (100% pentane then 1:9 EtOAc/pentane) providing six fractions: $\mathbf{A^1}$–$\mathbf{A^6}$. Fraction $\mathbf{A^1}$ consisted of **4.103**, and fraction $\mathbf{A^2}$ consisted of **4.104**. Fraction $\mathbf{A^3}$ was a complex mixture. Fractions $\mathbf{A^4}$–$\mathbf{A^6}$ contained mixtures of (±)-**4.99**, (±)-**4.100**, and *meso*-**4.100**.

Fraction **B** was purified by flash column chromatography using Sorbtech Premium Rf silica gel (100% pentane → 5% EtOAc/pentane → 10% EtOAc/pentane → 20% EtOAc/pentane) to provide five fractions: $\mathbf{B^1}$–$\mathbf{B^5}$. Fraction $\mathbf{B^1}$ was a complex mixture. Fractions $\mathbf{B^2}$–$\mathbf{B^3}$, and $\mathbf{B^5}$ contained mixtures of (±)-**4.99**, (±)-**4.100**, and *meso*-**4.100**. Fraction $\mathbf{B^4}$ was purified by flash column chromatography using Sorbtech Premium Rf silica gel (5:95 $Et_2O/CH_2Cl_2$) providing **4.101** (~3 mg, 6.6 x $10^{-3}$ mmol, 0.2% yield).

(±)-**4.99**, (±)-**4.100**, and *meso*-**4.100** were identified by comparison to the previously described independently synthesized material.

**Indole 4.101**

$R_f$ = 0.38 (5% EtOAc/pentane); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) δ 7.97–7.95 (m, 1H), 7.36 (s, 1H), 7.26 (d, *J* = 1.0 Hz, 1H), 7.08 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.42–3.38 (m, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.55 (d, *J* = 7.1 Hz, 2H), 1.66–1.63 (m, 4H), 1.65 (s, 9H), 1.55–1.50 (m, 4H), 1.39 (s, 9H), 1.19–1.15 (m, 3H); **$^{13}$C NMR** (125 MHz, $CD_2Cl_2$) δ 155.7, 135.6, 130.45, 130.43, 125.8, 123.2, 119.0, 117.6, 114.6, 83.2, 44.0, 40.2, 40.11, 40.09, 33.1, 31.6, 28.1, 27.9, 26.6, 26.3, 25.5; **HRMS** (ESI) calcd for $[C_{27}H_{40}N_2O_4 + Na]+$ 479.2880, found 479.2952. The structure was confirmed by COSY, HSQC, HMBC, and HSQC-TOCSY.

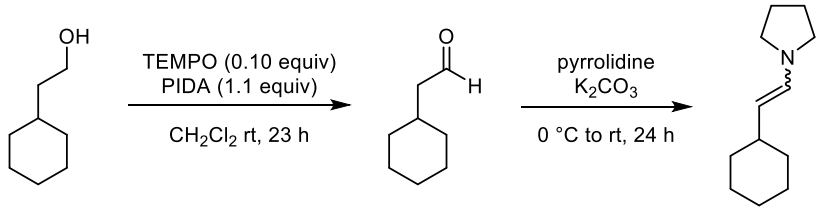
**1,2-Dicyclohexylethane 4.103**

$R_f$ = 0.81 (5% EtOAc/pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) 1.72–1.62 (m, 10H), 1.26–1.10 (m, 12H), 0.90–0.82 (m, 4H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 38.0, 34.8, 33.5, 26.8, 26.5. $^1$H NMR spectroscopic data of **4.103** are in excellent agreement with those reported in the literature [28]

[28] Liu, G.-B.; Zhao, H.-Y.; Dai, L.; Thiemann, T.; Tashiro, H.; Tashiro, M. *J. Chem. Res.* **2009**, *9*, 579.

**1,3-Dicyclohexylpropan-2-one 4.104**

$R_f$ = 0.50 (5% EtOAc/pentane); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 2.23 (d, *J* = 6.9 Hz, 4H), 1.85–1.77 (m, 2H), 1.68–1.63 (m, 12H), 1.31–1.22 (m, 4H), 1.17–1.09 (m, 4H), 0.94–0.86 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 210.9, 51.2, 33.8, 33.2, 26.2, 26.1. $^1$H NMR spectroscopic data of **4.104** are in excellent agreement with those reported in the literature.[29]




**4.130** **4.118** **4.128**

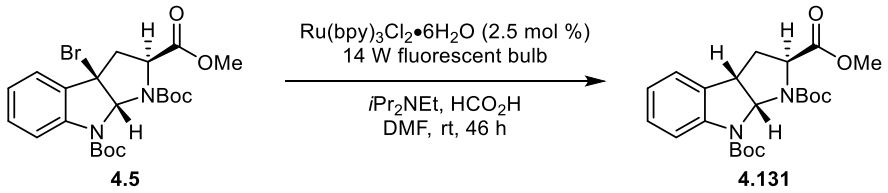
**2-Cyclohexylacetaldehyde 4.118**

A flask was charged with TEMPO (610 mg, 3.9 mmol, 0.10 equiv), PIDA (13.9 g, 42.9 mmol, 1.1 equiv), and 2-cyclohexylethanol (5.50 mL, 39.0 mmol, 1.0 equiv). $CH_2Cl_2$ (40.0 mL) was added, and the reaction mixture was allowed to stir at rt for 23 h. The reaction mixture was extracted with saturated aqueous $Na_2S_2O_3$ (2 x 50 mL), and the organic extract was stirred with 10% (w/w) aqueous $NaHSO_3$ (100 mL) for 2 h. The resulting white precipitate was vacuum filtered and washed with $CH_2Cl_2$ then stirred with $CH_2Cl_2$ (100 mL) and saturated aqueous $NaHCO_3$ (100 mL) for 3 h. The organic phase was concentrated *in vacuo*. The recovered $CH_2Cl_2$ and aqueous phase were combined, shaken, and the organic phase was concentrated (x2). This produced **4.118** as a colorless oil, which was used for the next step without further purification (2.07 g, 16.4 mmol, 42%).

[29] Wei, Y.; Rao, B.; Cong, X.; Zeng, X. *J. Am. Chem. Soc.* **2015**, *137*, 9250.

**1-(2-Cyclohexyl-1-ethenyl)pyrrolidine 4.128**

1-(2-Cyclohexylvinyl)pyrrolidine **4.128** was prepared from **4.118** according to Igarashi and Tada.[30] To aldehyde **4.118** (~0.55 g, 4.4 mmol, 1.0 equiv) and $K_2CO_3$ (0.60 g, 4.4 mmol, 1.0 equiv) at 0 °C was added pyrrolidine (0.73 mL, 8.7 mmol, 2.0 equiv), dropwise. The reaction mixture was allowed to warm to rt, stirring, over 23 h then syringe filtered, washed with benzene, and concentrated. **4.128** was isolated as a colorless oil (0.76 g, 4.2 mmol, 98%), stored at –20 °C, and used for the next step without further purification. **$^1$H NMR** (400 MHz, $CDCl_3$) δ 6.16 (dd, *J* = 13.8, 0.4 Hz, 1H), 4.11 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.96–2.93 (m, 4H), 2.87–2.84 (m, 1H), 1.84–1.81 (m, 4H), 1.71–1.67 (m, 6H), 1.28–1.03 (m, 4H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 133.9, 106.1, 49.2, 39.1, 35.3, 26.4, 26.3, 24.8; **IR** (thin film) 2293, 2850, 1651 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{12}H_{21}N + H]^+$ 180.1747, found 180.1764.

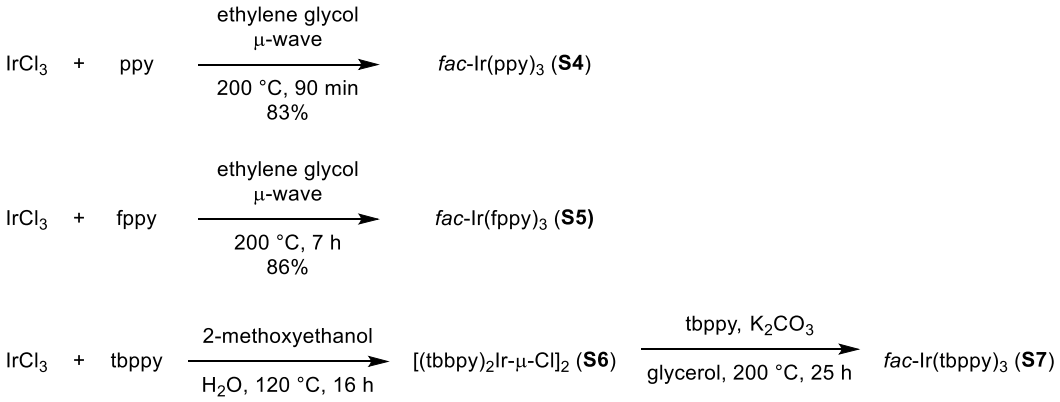



**Tetrahydropyrrolo[2,3-*b*]indole 4.131**

To $Ru(bpy)_3Cl_2•6H_2O$ (56.8 mg, 0.075 mmol, 2.5 mol %) in a $N_2$-purged 100-mL flask was added a solution of bromopyrroloindoline **4.5** (1.50 g, 3.0 mmol, 1.0 equiv) in DMF (30.0 mL). *i*PrNEt (5.2 mL, 30.0 mmol, 10.0 equiv) and formic acid (1.1 mL, 30.0 mmol, 10.0 equiv) were added, and the reaction mixture was sparged with $N_2$ for 20 min. A 14W fluorescent hand-held lamp was placed within 10 cm of the reaction flask, and a reflective box was placed over the flask and lamp. The reaction mixture was allowed to stir at rt, irradiated, for 46 h. The reaction mixture was diluted with $Et_2O$ (100 mL) and $H_2O$ (100 mL). The aqueous phase was extracted with $Et_2O$ (4 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:4 EtOAc/hexanes x 2) provided **4.131** as a white

[30] Igarashi, M.; Tada, M. *J. Heterocyclic Chem.* **1995**, *32*, 807.

solid (818 mg, 1.95 mmol, 65%). $R_f$ = 0.2 (1:4 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.55–7.53 (br s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.04 (d, 7.5 Hz, 1H), 6.37 (d, *J* = 5.9 Hz, 1H), 3.96 (dt, *J* = 10.0 Hz, 6.6, 2H), 3.72 (s, 3H), 2.54 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.31–2.25 (m, 1H), 2.17 (s, 9H), 1.40 (s, 9H).




*fac*-Ir(ppy)$_3$ (**S4**) was prepared from $IrCl_3$•x$H_2O$ and ppy following Kawanishi et al.[31]

fppy and tbppy were prepared from 2-chloropyridine and the corresponding boronic acid (4-fluorophenyl boronic acid and 4-*tert*-butylphenyl boronic acid, respectively) following Weaver, et al.[32]

### *fac*-Ir(fppy)$_3$ S5

$IrCl_3$•x$H_2O$ (57 mg, 0.10, 1.0 equiv, 53% metal) and fppy (138 mg, 0.80 mmol, 8.0 equiv) in ethylene glycol (3.2 mL) were heated in a microwave reactor at 200 °C in 1 h increments for 7 h. The reaction mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic extracts were filtered through a pad of Celite and concentrated *in vacuo*. Purification by column chromatography (100% $CH_2Cl_2$) provided *fac*-Ir(fppy)$_3$ as a canary yellow powder (60.7 mg, 0.086 mmol, 86%). $R_f$ = 0.8 (100% $CH_2Cl_2$); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) 7.85 (d, *J* = 8.2 Hz, 3H), 7.67–7.63 (m, 6H), 7.51–7.49 (m, 3H), 6.91 (ddd, *J* = 7.2, 5.7 Hz, 1.4, 3H), 6.60 (td, *J* = 8.7, 2.7 Hz, 3H),

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[31] Abe, T.; Miyazawa, A.; Konno, H.; Kawanishi, Y. *Chem. Phys. Lett.* **2010**, *491*, 199.
[32] Singh, A.; Teegardin, K.; Kelly, M.; Prasad, K. S.; Krishnan, S.; Weaver, J. D. *J. Organometal. Chem.* **2015**, *776*, 51.

6.37 (dd, *J* = 10.3, 2.7 Hz, 3H); **$^{13}$C NMR** (125 MHz, $CD_2Cl_2$) δ 165.3, (d, *J* = 5.0 Hz), 163.1, 147.2, 140.2 (d, *J* = 2.5 Hz), 136.6, 125.8 (d, *J* = 8.8 Hz), 122.0, 121.8 (d, *J* = 16.4 Hz), 118.9, 107.4 (d, *J* = 23.8 Hz); **IR** (thin film) 3042, 1590, 1550, 1473, 1453, 1432, 1182, 1159 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{33}H_{21}F_3IrN_3 + Na]^+$ 732.1209, found 732.1241. The spectroscopic data of **S5** are in excellent agreement with those reported in the literature.[32,33]

**[(tbppy)$_2$Ir-μ-Cl]$_2$ S6**

To $IrCl_3$•x$H_2O$ (450 mg, 0.80 mmol, 1.0 equiv) and tbppy (380 mg, 1.80 mmol, 2.25 equiv) were added 2-methoxyethanol (26.0 mL) and $H_2O$ (10.0 mL). The reaction mixture was refluxed at 120 °C for 16 h then cooled to rt. The yellow precipitate was collected by vacuum filtration, washed with $H_2O$, and dried. **S6** was carried into the next reaction without further purification.

***fac*-Ir(tbppy)$_3$ S7**

**S6** (~500 mg, 0.40 mmol, 0.5 equiv), tbppy (200 mg, 0.95 mmol, 1.2 equiv), and potassium carbonate (557 mg, 4.0 mmol, 5.0 equiv) in glycerol (16.0 mL) were refluxed at 200 °C for 25 h. The reaction mixture was cooled to rt and diluted with $H_2O$ (25 mL). The yellow precipitate was vacuum filtered and washed with MeOH (20 mL), $Et_2O$ (20 mL), and hexanes (20 mL). Purification by flash column chromatography (50% $CH_2Cl_2$/hexanes) provided *fac*-Ir(tbppy)$_3$ as a yellow powder (442 mg, 0.54 mmol, 67% over two steps). $R_f$ = 0.9 (100% $CH_2Cl_2$). **$^1$H NMR** (400 MHz, $CDCl_3$) 7.79 (d, *J* = 8.0 Hz, 3H), 7.57–7.50 (m, 9H), 6.88–6.79 (m, 9H), 1.09 (s, 27H); **IR** (thin film) 2957, 1599, 1584, 1465, 1427, 1118 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{45}H_{48}IrN_3 + H]^+$ 824.3550, found 823.3531. $^1$H NMR spectroscopic data of **S7** are in excellent agreement with those reported in the literature.[32]

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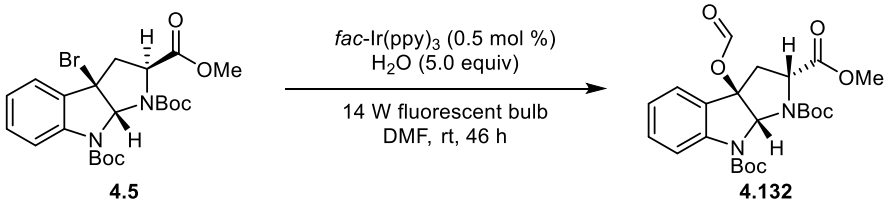
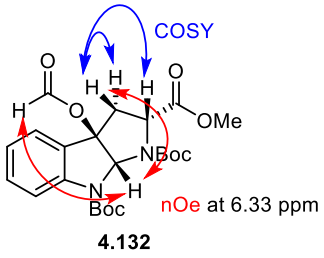
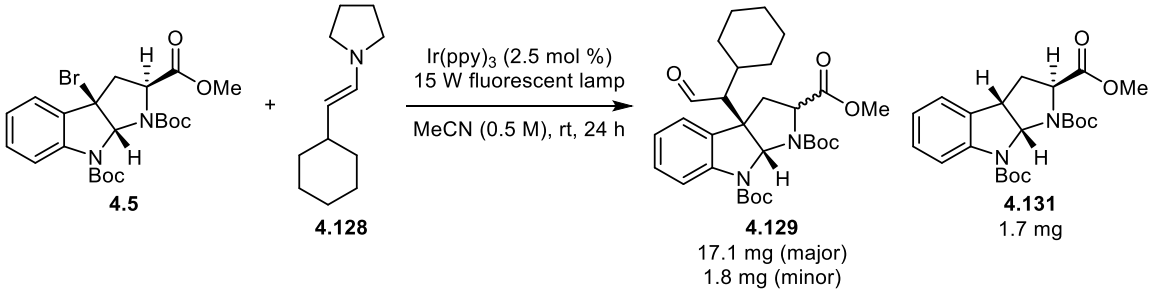
[33] Uraguchi, D.; Kinoshita, N.; Kizu, T.; Ooi, T. *J. Am. Chem. Soc.* **2015**, *137*, 13768.




**Formate ester 4.132**

To a 0.5-dram crimp-top vial in a nitrogen-filled glovebox was added bromopyrroloindoline **4.5** (50.0 mg, 0.10 mmol, 1.0 equiv), *fac*-Ir(ppy)$_3$ (0.4 mg, 6.1 x $10^{-4}$ mmol, 0.5 mol %), degassed $H_2O$ (9.0 μL, 0.50 mmol, 5.0 equiv), and DMF (0.20 mL). The vial was sealed with a PTFE-lined cap and removed from the glovebox. The reaction mixture irradiated with a 15 W fluorescent lamp, stirring, for 26 h. The reaction mixture was diluted with $Et_2O$ and concentrated *in vacuo*. Purification by flash column chromatography (1:3 EtOAc/hexanes) provided **4.132** (13.3 mg, 0.03 mmol, 29%) along with recovered **4.5** (8.4 mg, 0.02 mmol, 17%). $R_f$ = 0.25 (1:3 EtOAc/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) 7.87 (s, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.33 (s, 1H), 3.97 (t, *J* = 8.3 Hz, 1H), 3.74 (s, 3H), 2.53 (dd, *J* = 12.4, 10.6 Hz, 1H), 1.58 (s, 9H), 1.40 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 172.0, 158.9, 152.3, 144.13, 131.2, 125.9, 123.9, 100.0, 87.9, 82.1, 80.1, 59.0, 52.3, 36.8, 29.7, 28.4, 28.5, 28.2, 25.6; **IR** (thin film) 2979, 2931, 2254, 1724, 1605 cm$^{-1}$; **HRMS** (ESI) calc for $[C_{23}H_{30}N_2O_8 + Na]^+$ 485.1894, found 485.1898. The structure was confirmed by COSY, HMQC, HMBC, and nOe at 6.33 ppm.






**Photoredox catalyzed α-alkylation of 4.128 with 4.5**

In a nitrogen-filled glovebox, bromopyrroloindoline **4.5** (199 mg, 0.40 mmol, 1.0 equiv), and enamine **4.128** (453 mg, 2.5 mmol, 5.0 equiv) in MeCN (0.80 mL) were divided equally into four 0.5-dram crimp-top vials each containing *fac*-Ir(ppy)$_3$ (1.3 mg, 0.002 mmol, 2.0 mol %). The vials were sealed with PTFE-lined caps and removed from the glovebox. The reaction mixtures were irradiated with a 15 W fluorescent lamp, stirring, for 4 days. The reaction mixtures were combined and concentrated *in vacuo*. Purification by flash column chromatography using Sorbtech Premium Rf silica gel (1:1 $Et_2O$/hexanes) provided three fractions: **A**, **B**, and **C**. Fraction **B** was purified by flash column chromatography using Sorbtech Premium Rf silica gel (50% $Et_2O$/hexanes) providing three fractions: **B$^1$** (1.8 mg), **B$^2$** (17.1 mg), and **B$^3$**. **B$^3$** was identified as **4.131** (1.7 mg). **B$^2$** was desired *exo*-**4.129** (17.1 mg, 0.03 mmol, 8%).

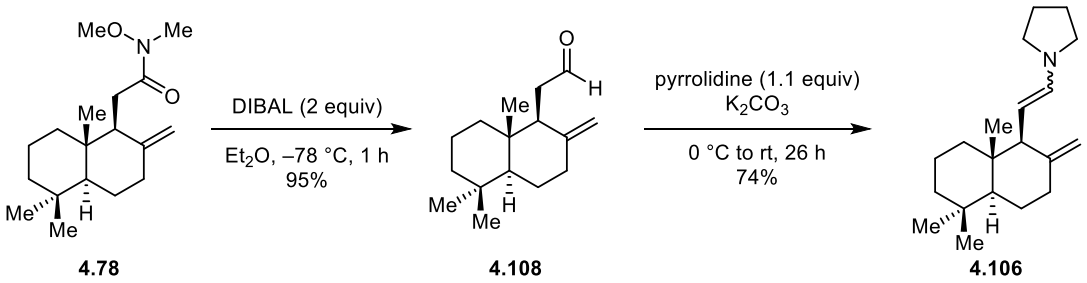
***Endo*-Aldehyde 4.129 (B$^1$, minor product)**

$R_f$ = 0.27 (1:1 $Et_2O$/hexanes); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) δ 9.44 (d, *J* = 3.8 Hz, 1H), 7.45 (br s, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.25 (td, *J* = 7.42, 6.1 Hz, 1H), 6.10 (s, 1H), 3.80–3.75 (m, 1H), 3.63 (s, 3H), 2.62–2.58 (m, 2H), 2.31 (t, *J* = 4.0 Hz, 1H), 2.09 (dd, *J* = 12.7, 10.1 Hz, 1H), 1.74–1.40 (m, 29H). The structure was confirmed by COSY, HMQC, HMBC, and nOe (9.45, 6.09 ppm).

***Exo*-Aldehyde 4.129 (B$^2$, major product)**

$R_f$ = 0.37 (1:1 $Et_2O$/hexanes); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) δ 9.65 (d, *J* = 2.3 Hz, 1H), 7.39 (br s, 1H), 7.30–7.26 (m, 1H), 7.20–7.16 (m, 1H), 6.98 (quin, *J* = 8.28 Hz, 1H), 6.03

(s, 1H), 3.77–3.73 (m, 1H), 3.6 (s, 3H), 2.82–2.75 (m, 1H), 2.45 (app s, 1H), 2.01 (dd, *J* = 12.8, 10.5 Hz, 1H), 1.66–1.63 (m, 3H), 1.57–1.54 (m, 25H). The structure was confirmed by COSY, HMQC, and HMBC.




**4.78** **4.108** **4.106**

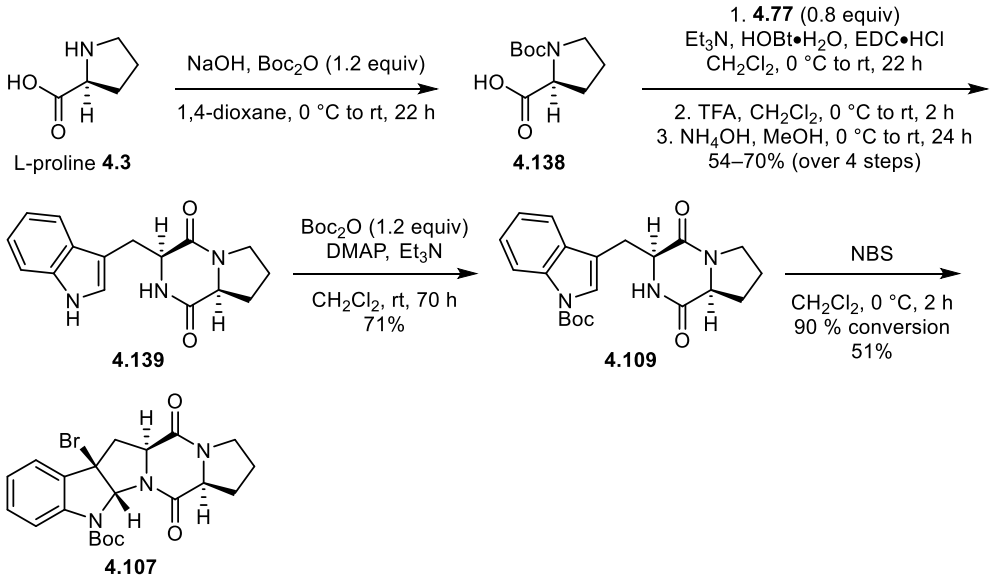
**Aldehyde 4.108**

To Weinreb amide **4.78** (1.31 g, 4.5 mmol, 1.0 equiv) in $Et_2O$ (56.0 mL) at –78 °C was added, dropwise, DIBAL (9.0 mL, 8.9 mmol, 2.0 equiv, 1.0 M in toluene). The reaction mixture was allowed to stir at –78 °C for 1 h. The reaction mixture was quenched with EtOAc (25 mL) and saturated aqueous sodium potassium tartrate (50 mL) and allowed to warm to rt overnight. The reaction mixture was diluted with $H_2O$ (30 mL), and the aqueous phase was extracted with $Et_2O$ (2 x 30 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (1:3 $Et_2O$/hexanes) provided **4.108** as a white solid (1.00 g, 4.3 mmol, 95%). $R_f$ = 0.66 (1:3 $Et_2O$/hexanes); **$^1$H NMR** (400 MHz, $CDCl_3$) 9.64–9.63 (m, 1H), 4.82 (s, 1H), 4.39 (s, 1H), 2.55–2.34 (m, 2H), 2.10 (dd, *J* = 2.9, 2.5 Hz, 1H), 1.76 (ddt, *J* = 10.3, 5.1, 2.5 Hz, 1H), 1.59–1.40 (m, 6H), 1.34 (td, *J* = 12.9, 4.3 Hz, 1H), 1.24–1.17 (m, 1H), 1.13–1.06 (m, 1H), 0.90 (s, 3H), 0.82 (s, 3H), 0.71 (s, 3H). The $^1$H NMR spectroscopic data of **3.111** are in excellent agreement with those reported in the literature.[11]

**Enamine 4.106**

To aldehyde **4.108** (476 mg, 2.0 mmol, 1.0 equiv) and $K_2CO_3$ (296 mg, 2.1 mmol, 1.1 equiv) at 0 °C was added pyrrolidine (0.19 mL, 2.2 mmol, 1.1 equiv) dropwise. The reaction mixture was stirred, warming to rt, for 24–72 h. The reaction mixture was

diluted with $Et_2O$, syringe filtered, and concentrated. Purification by column chromatography (1:3 EtOAc/hexanes) provided **4.106** as a colorless oil (362 mg, 1.26 mmol, 62%). $R_f$ = 0.56 (1:3 $Et_2O$/hexanes); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.06 (d, *J* = 13.6 Hz, 1H), 4.70 (dd, *J* = 14.4, 1.8 Hz, 2H), 4.10 (dd, *J* = 13.6, 9.8 Hz, 1H), 3.00 (t, *J* = 6.59 Hz, 4H), 2.44 (ddd, *J* = 13.3, 4.4, 2.2 Hz, 1H), 2.11–2.08 (m, 1H), 1.85–1.83 (m, 4H), 1.68 (dtd, *J* = 10.3, 5.2, 2.5 Hz, 1H), 1.61–1.58 (m, 1H), 1.56–1.46 (m, 1H), 1.38 (d, *J* = 14.4 Hz, 3H), 1.33 (dd, *J* = 13.0, 4.4Hz, 1H), 1.17 (td, *J* = 13.5, 4.2 Hz, 1H), 1.08 (dd, *J* = 12.6, 2.7 Hz, 1H), 0.93 (td, *J* = 13.5, 3.4 Hz, 1H), 0.88 (s, 3H), 0.82 (s, 3H), 0.73 (s, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 152.2, 137.1, 107.4, 96.0, 59.5, 55.2, 49.4, 42.5, 40.9, 39.2, 36.9, 33.6, 33.57, 24.8, 23.6, 22.0, 19.3, 14.7; **HRMS** (ESI) calcd for $[C_{20}H_{33}N + H]^+$ 288.2686, found 288.3312.




*N*-Boc-L-proline **4.138** was prepared from L-proline (**4.3**) according to Ferreira et al.[34]

### *Cyclo*-L-proline-L-tryptophan 4.139

To L-tryptophan methyl ester **4.77** (3.0 g, 12.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (120.0 mL) at

[34] Knight, B. J.; Stache, E. E.; Ferreira, E. M. *Org. Lett.* **2014**, *16*, 432.

0 °C was added sequentially $Et_3N$ (7.5 mL, 54.0 mmol, 4.5 equiv), HOBt•$H_2O$ (3.0 g, 18.0 mmol, 1.5 equiv), **4.138** (3.3 g, 15.3 mmol, 1.3 equiv), and EDC•HCl (3.44 g, 18.0 mmol, 1.5 equiv). The reaction mixture was allowed to stir, warming to rt over 22 h then quenched with aqueous HCl (1 M, 260 mL). The aqueous layer was extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 100 mL), and the aqueous phase was back-extracted with $CH_2Cl_2$ (2 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The crude product was dissolved in $CH_2Cl_2$ (60.0 mL) and cooled to 0 °C. TFA (17.5 mL) was added dropwise, and the reaction mixture was allowed stir at rt for 2 h. The reaction mixture was concentrated *in vacuo* then dissolved in MeOH (47.0 mL) and cooled to 0 °C. $NH_4OH$ (7.7 mL, 28–30% in $H_2O$) was added dropwise, and the reaction mixture was allowed to warm to rt, stirring, for 24 h. The reaction mixture was concentrated *in vacuo* to remove the MeOH then dissolved in $CH_2Cl_2$ (50 mL) and $H_2O$ (50 mL). The organic phase was extracted with $H_2O$ (2 x 50 mL), and the combined aqueous extracts were back-extracted with $CH_2Cl_2$ (100 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered, and concentrated. Recrystallization from MeOH provided **4.139** as an off-white powder (1.78 g, 6.3 mmol, 54%). $R_f$ = 0.4 (3:7 acetone/$Et_2O$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 5.90 (s, 1H), 4.35 (dd, *J* = 10.5, 3.0 Hz, 1H), 4.04 (t, *J* = 7.8 Hz, 1H), 3.73 (dd, *J* = 15.1, 3.8 Hz, 1H), 3.65–3.56 (m, 2H), 2.98 (dd, *J* = 15.1, 10.5 Hz, 1H), 2.30 (dt, *J* = 10.4, 6.6 Hz, 1H), 2.01–1.84 (m, 3H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 169.3, 165.5, 136.6, 126.7, 123.5, 122.5, 119.7, 118.4, 111.5, 109.5, 59.1, 54.6, 45.3, 28.2, 26.7, 22.5; **IR** (thin film) 3286, 3055, 2981, 2945, 2873, 1677, 1555 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{16}H_{17}N_3O_2 + Na]^+$ 306.1213, found 306.1379; $[\alpha]_{589}^{20.0}$ = –146.3 (c = 0.01 g $mL^{-1}$, $CH_2Cl_2$).

**_N_-Boc-*cyclo*-L-proline-L-tryptophan 4.109**

To *cyclo*-L-proline-L-tryptophan **4.139** (1.78 g, 6.3 mmol, 1.0 equiv), DMAP (156 mg, 1.3 mmol, 0.2 equiv), and $Et_3N$ (1.75 mL, 7.5 mmol, 1.2 equiv) in $CH_2Cl_2$ (210 mL) at rt

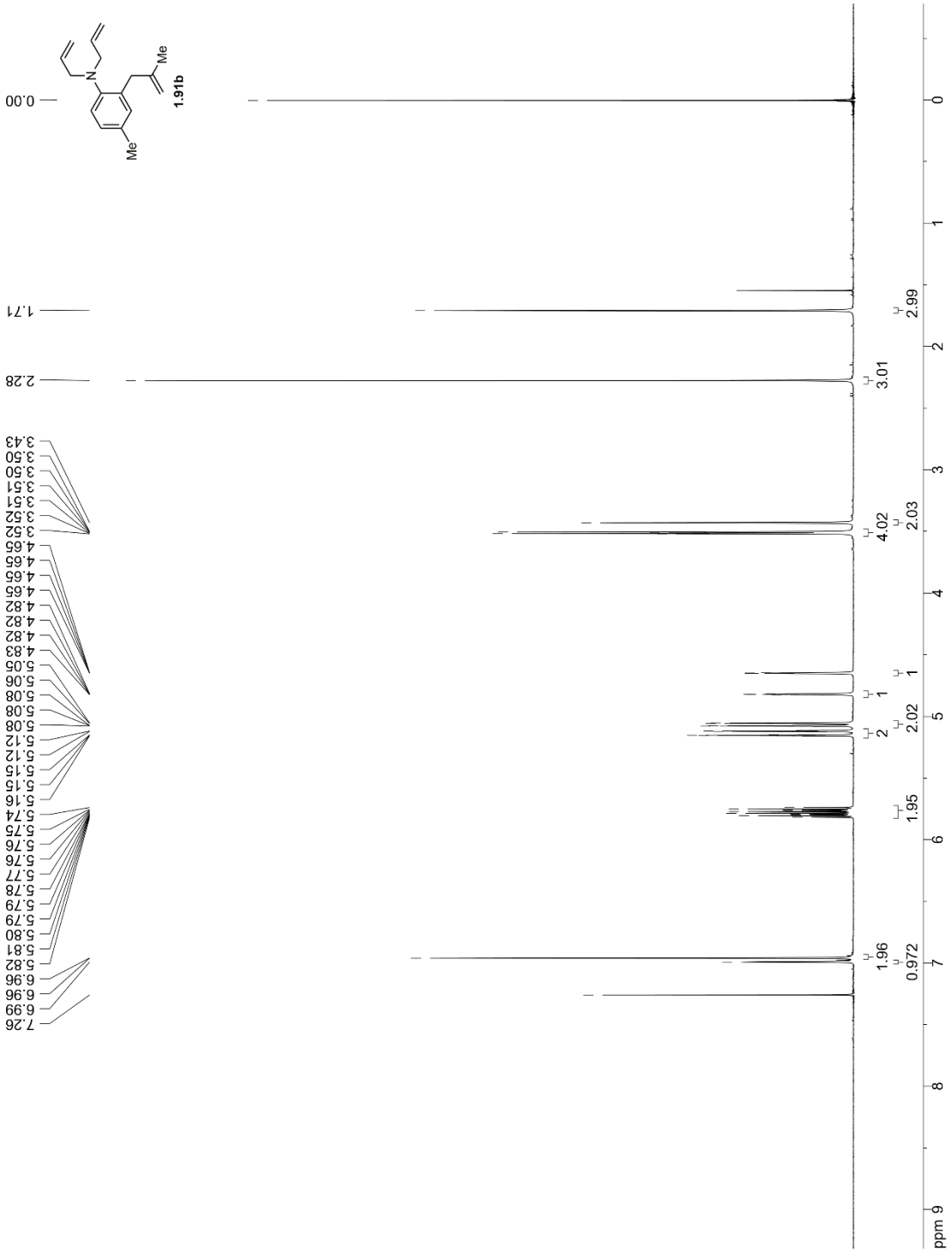
was added $Boc_2O$ (1.76 g, 8.1 mmol, 1.3 equiv). The reaction mixture was allowed to stir at rt for 3 days. The reaction mixture was extracted with saturated aqueous $NaHCO_3$ (2 x 50 mL) and $H_2O$ (2 x 50 mL). The organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography (5:95 MeOH/$CH_2Cl_2$) provided **4.109** as a white foam (1.81 g, 4.7 mmol, 75%). $R_f$ = 0.55 (5:95 MeOH/$CH_2Cl_2$); **$^1$H NMR** (500 MHz, $CD_2Cl_2$) δ 8.13 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 5.81 (s, 1H), 4.37 (dd, *J* = 10.5, 3.2 Hz, 1H), 4.04 (t, *J* = 7.8 Hz, 1H), 3.65–3.48 (m, 3H), 2.89 (dd, *J* = 15.3, 10.6 Hz, 1H), 2.25 (dt, *J* = 10.8, 5.6 Hz, 1H), 1.92 (m, 3H), 1.65 (s, 9H); **$^{13}$C NMR** (125 MHz, $CD_2Cl_2$) δ 169.4, 165.0, 149.4, 135.8, 129.7, 124.7, 124.6, 122.6, 118.7, 115.4, 115.0, 83.8, 59.1, 45.3, 28.2, 27.9, 27.4, 26.4, 22.6; **IR** (thin film) 3227, 3054, 2980, 2884, 1731, 1673, 1453, 1371 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{21}H_{25}N_3O_4 + Na]^+$ 406.1737, found 406.1792; $[\alpha]_{589}^{20.0}$ = –59.5 (c = 0.01 g $mL^{-1}$, $CH_2Cl_2$).

**Bromopyrroloindoline 4.107**

*N*-Boc-*cyclo*-L-proline-L-tryptophan **4.109** (1.80 g, 4.7 mmol, 1.0 equiv) in $CH_2Cl_2$ (120.0 mL) was divided into two 100-mL flasks. To each of these at 0 °C was added NBS (0.42 g, 2.4 mmol, 1.0 equiv). The reaction mixtures were allowed to stir at 0 °C for 2 h then quenched with saturated aqueous $NaHCO_3$ (20 mL each) and allowed to warm to rt. The reaction mixtures were combined, and the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with brine, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (3:7 acetone/$Et_2O$) provided **4.107** as an orange foam (868 mg, 1.88 mmol, 40%). $R_f$ = 0.45 (3:7 acetone/$Et_2O$); **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.1 Hz, 1H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.28–7.25 (m, 1H), 7.08 (t, *J* = 2.55 Hz, 1H), 6.28 (s, 1H), 4.38 (dd, *J* = 10.2, 3.5 Hz, 1H), 4.02 (t, *J* = 8.0 Hz, 1H), 3.81 (dd, *J* = 14.2, 3.6 Hz, 1H), 3.35 (td, *J* = 7.7, 4.1 Hz, 1H), 3.20–3.16 (m, 1H), 3.09 (dd, *J* = 14.2, 10.2, 1H), 2.21–2.01 (m, 2H), 1.82–1.79 (m, 2H), 1.64 (s, 9H); **$^{13}$C NMR** (125 MHz, $CDCl_3$) δ 166.7, 164.3, 151.7, 139.9, 132.8, 130.5, 124.8, 124.3, 116.8, 100.0, 84.7, 82.5, 60.6, 60.5, 59.1, 45.1, 37.6, 28.3, 27.3,

23.3; **IR** (thin film) 3055, 2984, 2885, 2306, 1776, 1716, 1678, 1266, 1152 $cm^{-1}$; **HRMS** (ESI) calcd for $[C_{21}H_{24}BrN_3O_4 + H]^+$ 462.1023, found 462.1079. The structure was confirmed by COSY, HMQC, and HMBC.

# Appendix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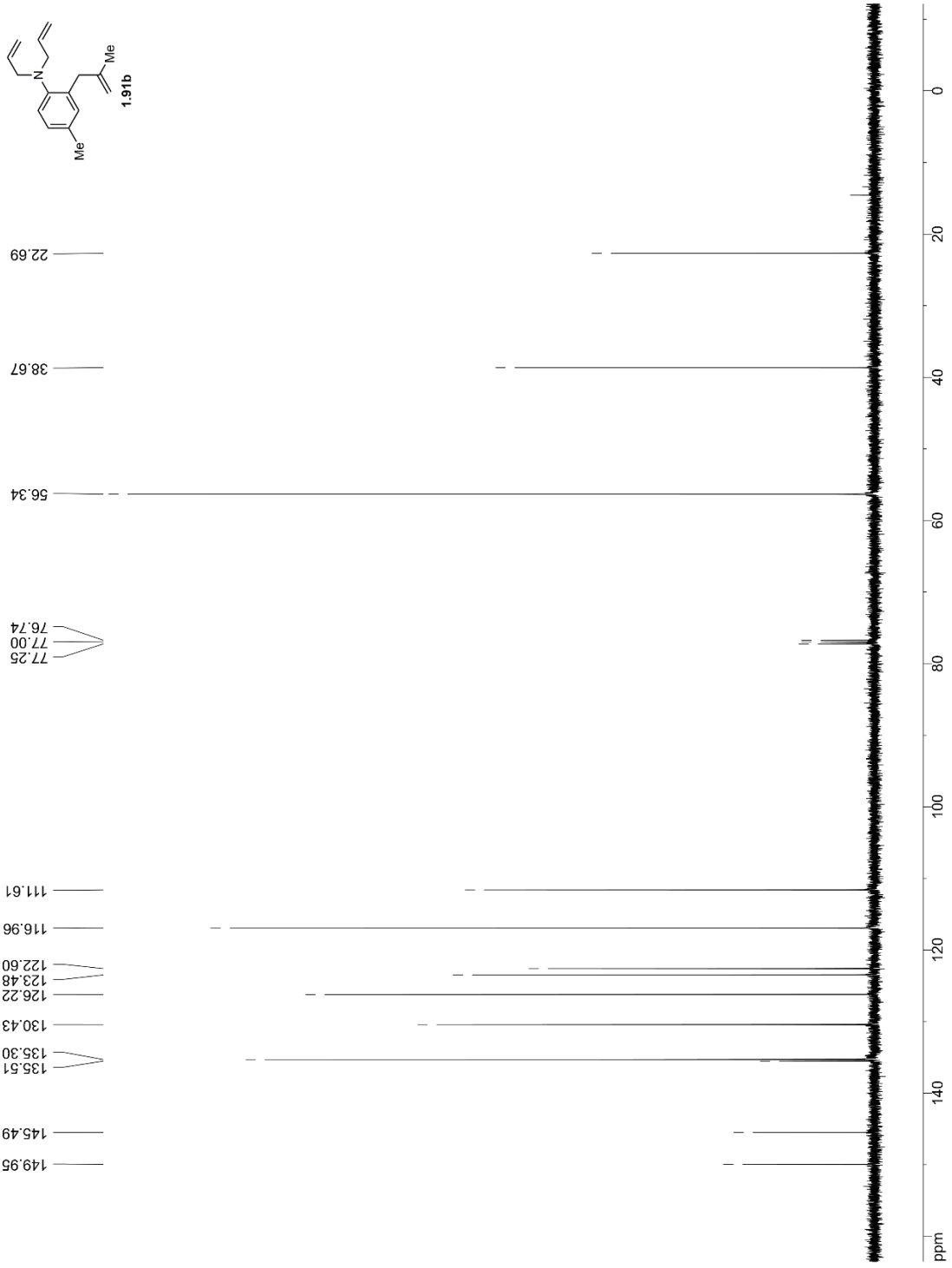
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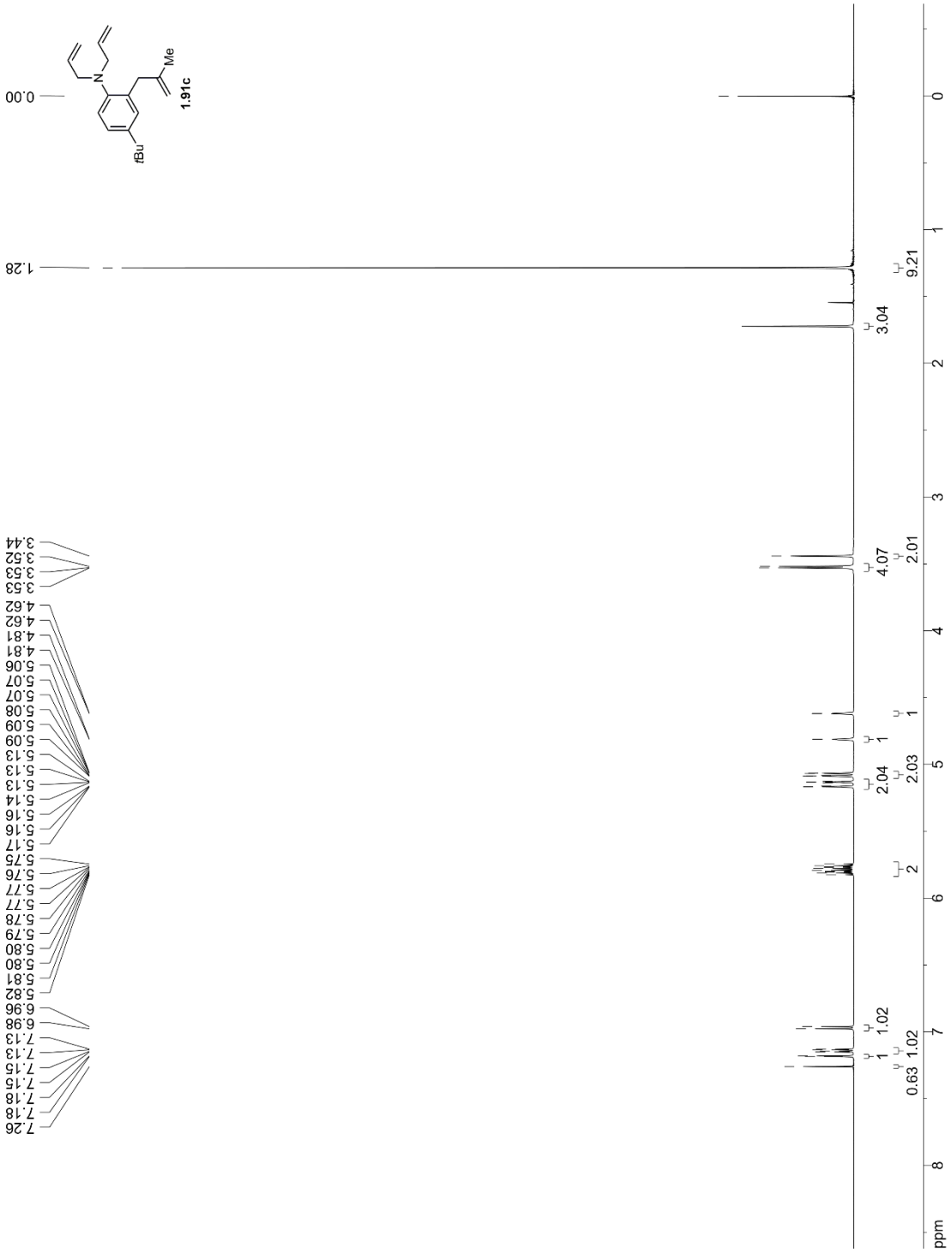
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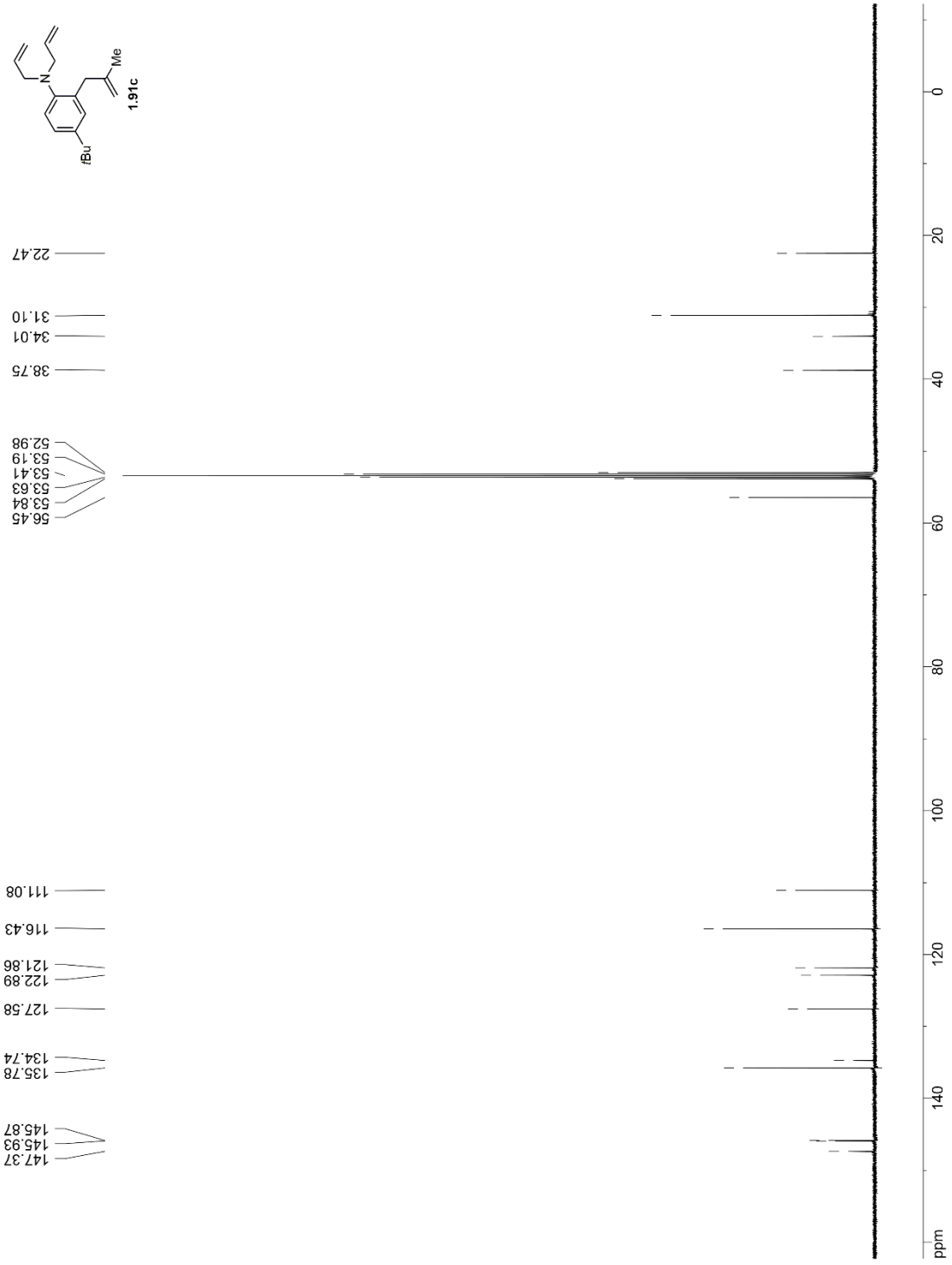
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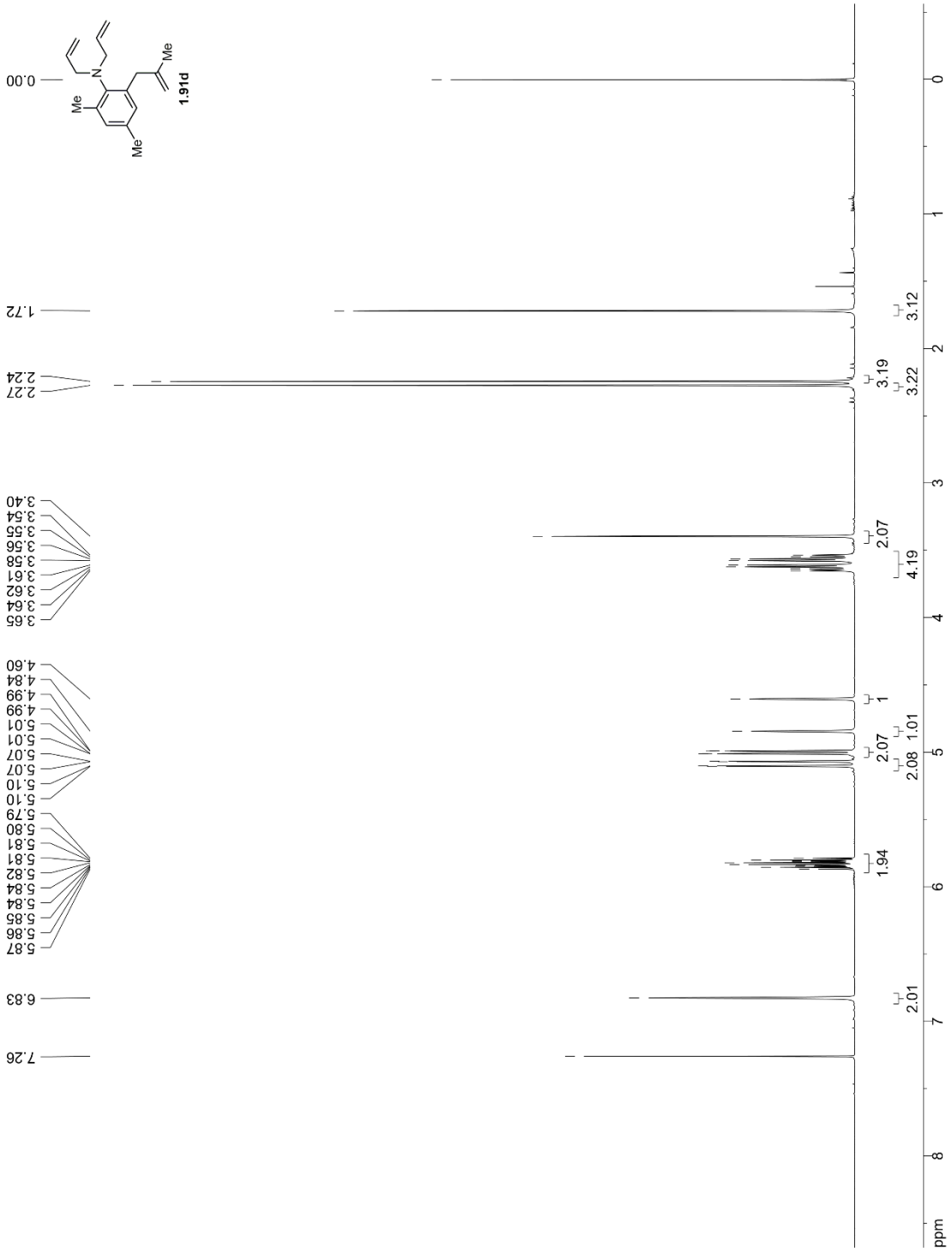
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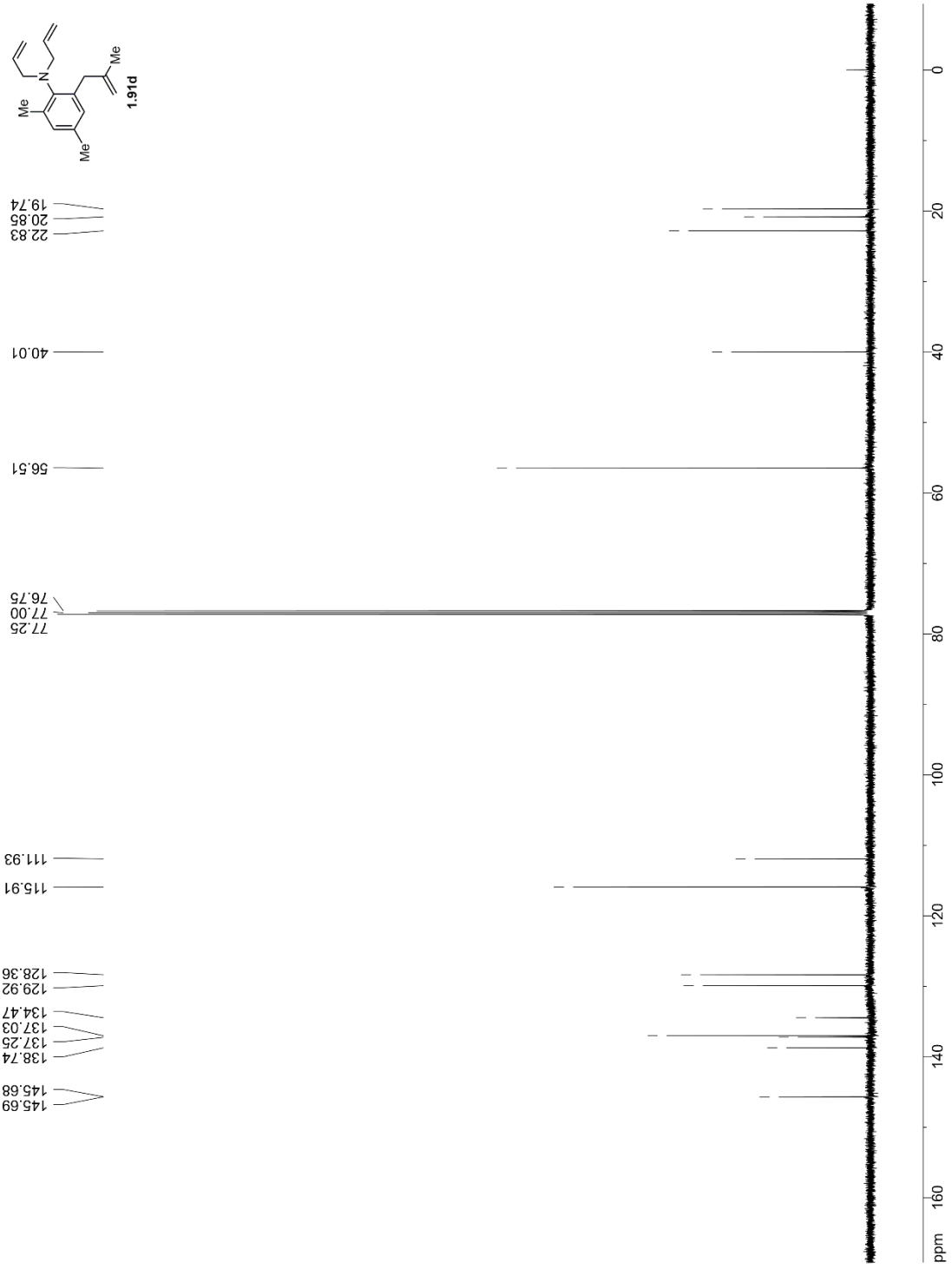
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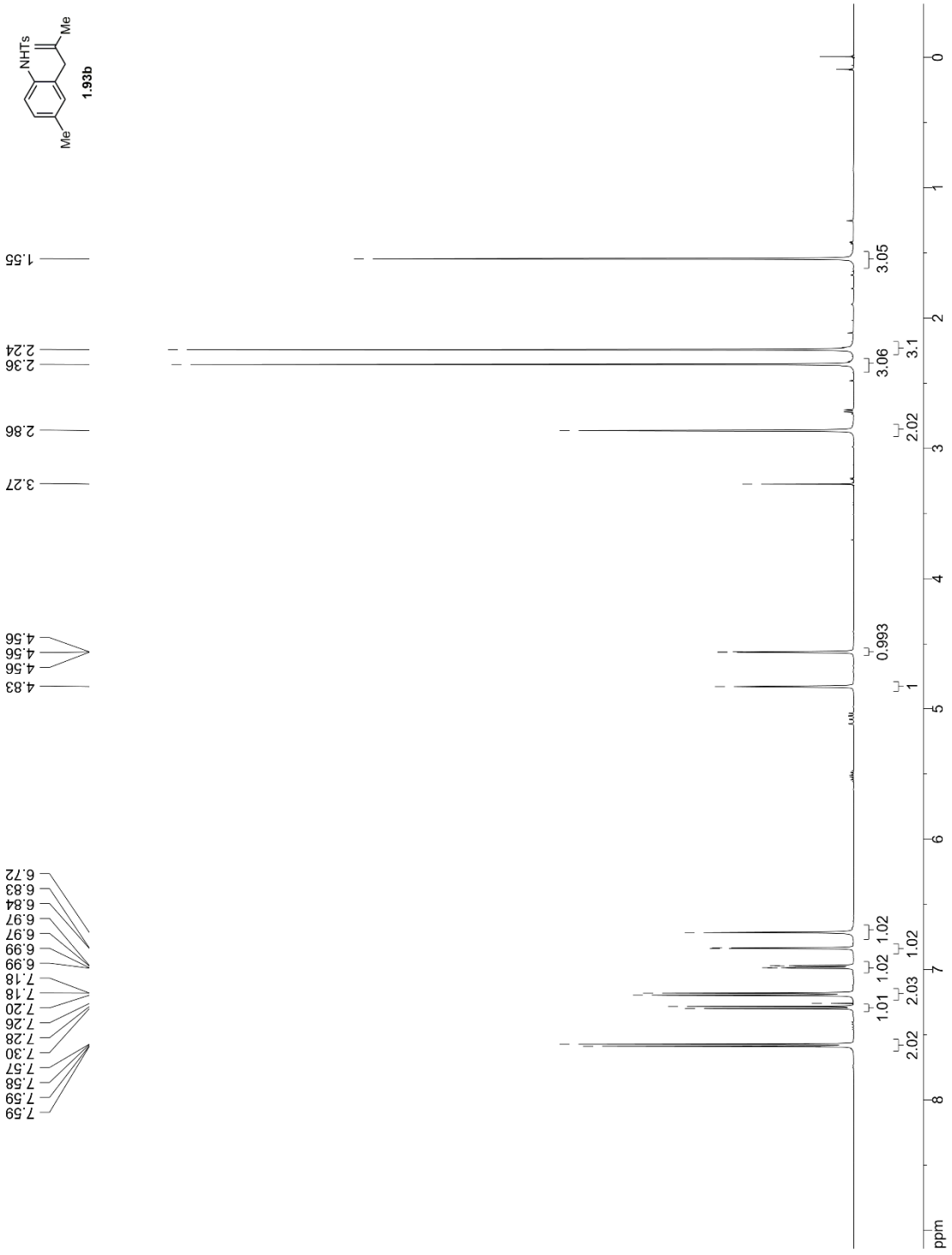
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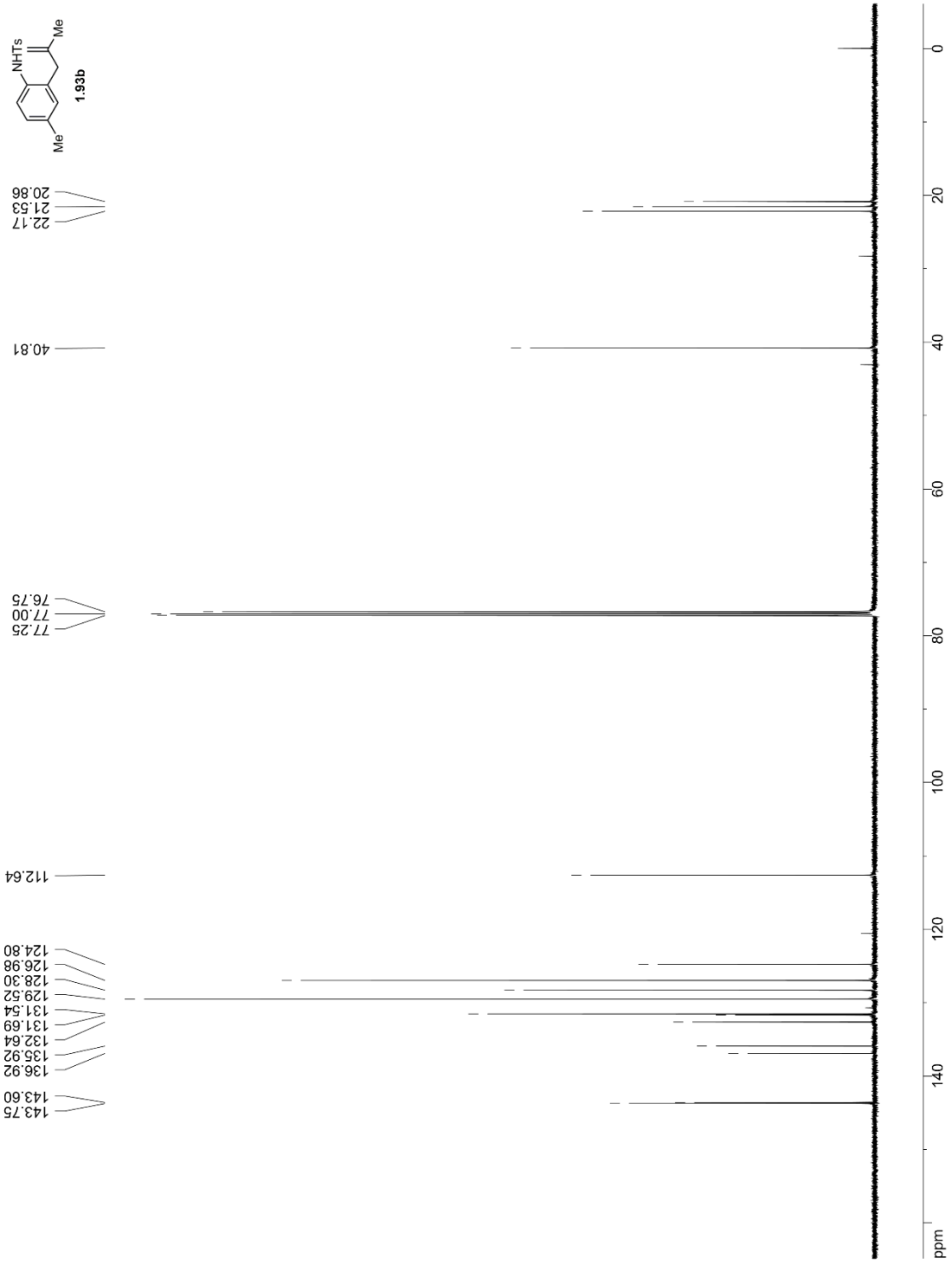
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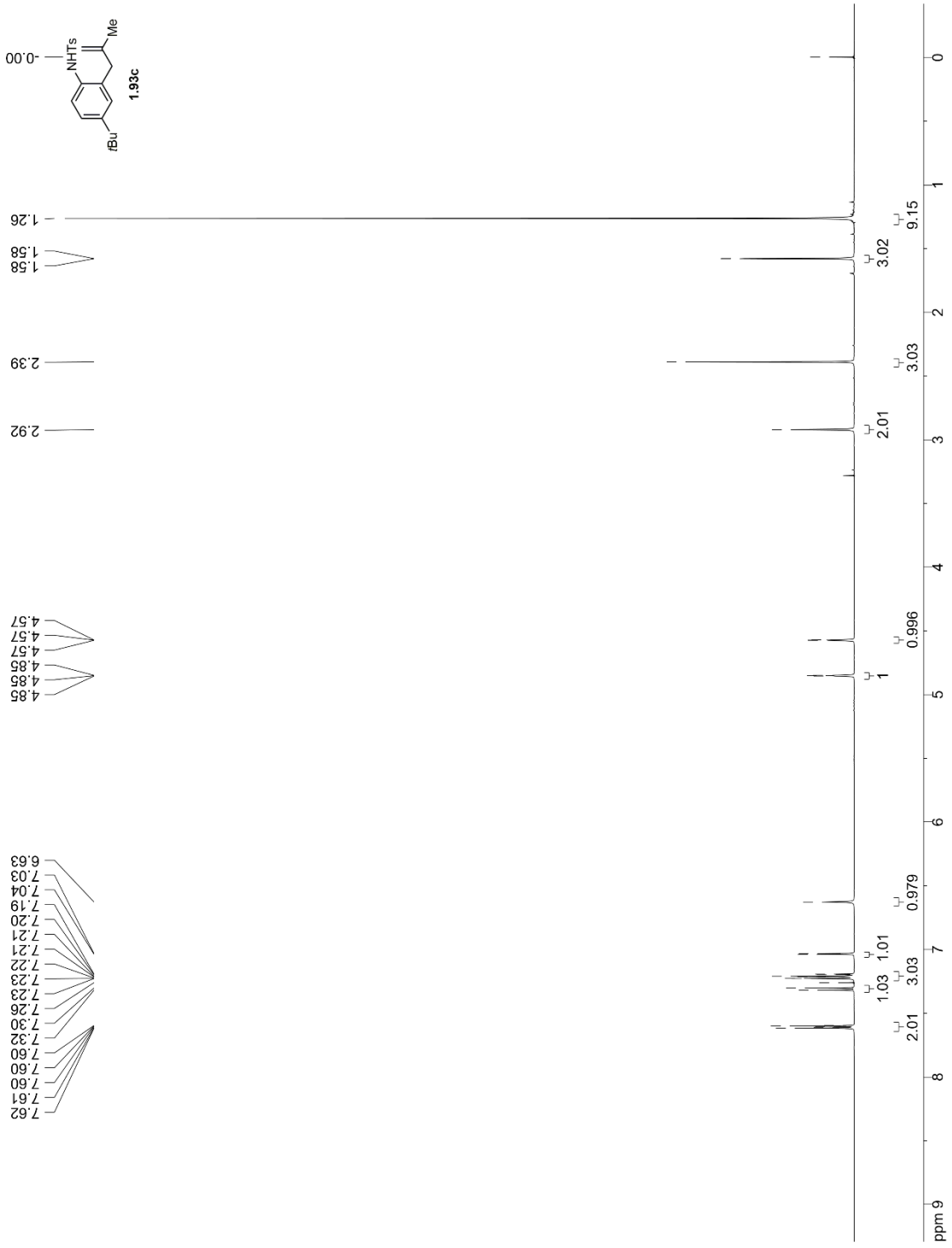
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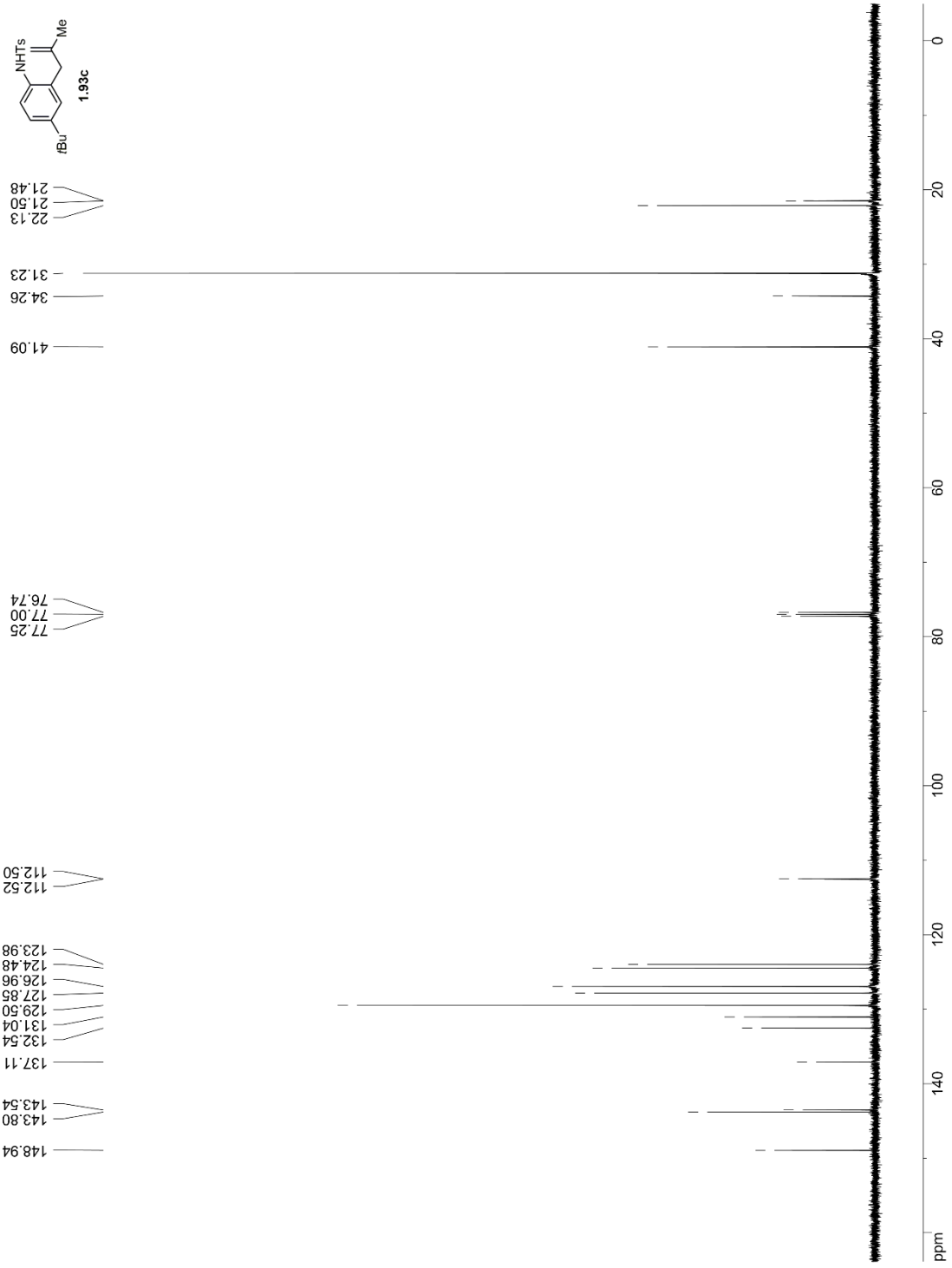
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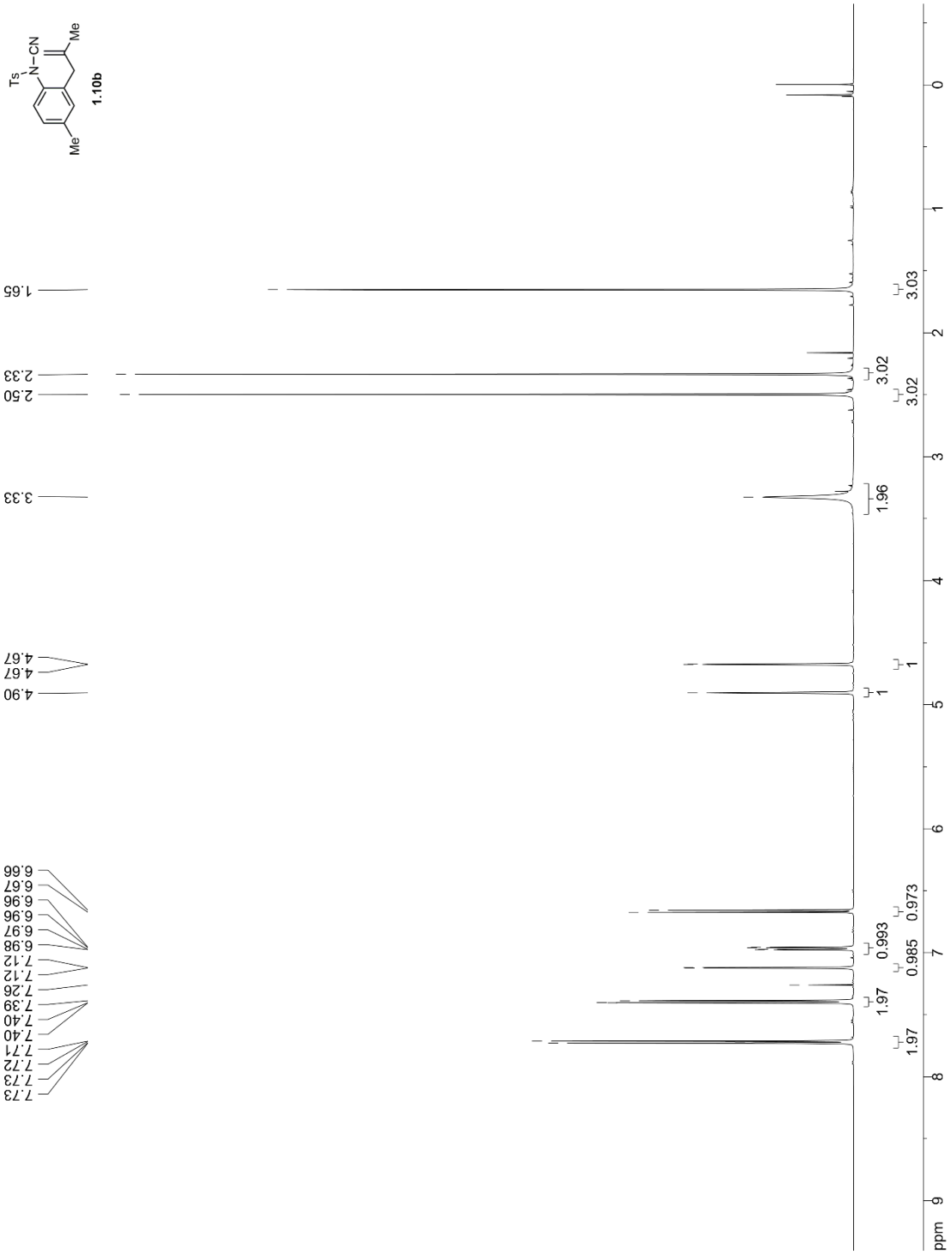
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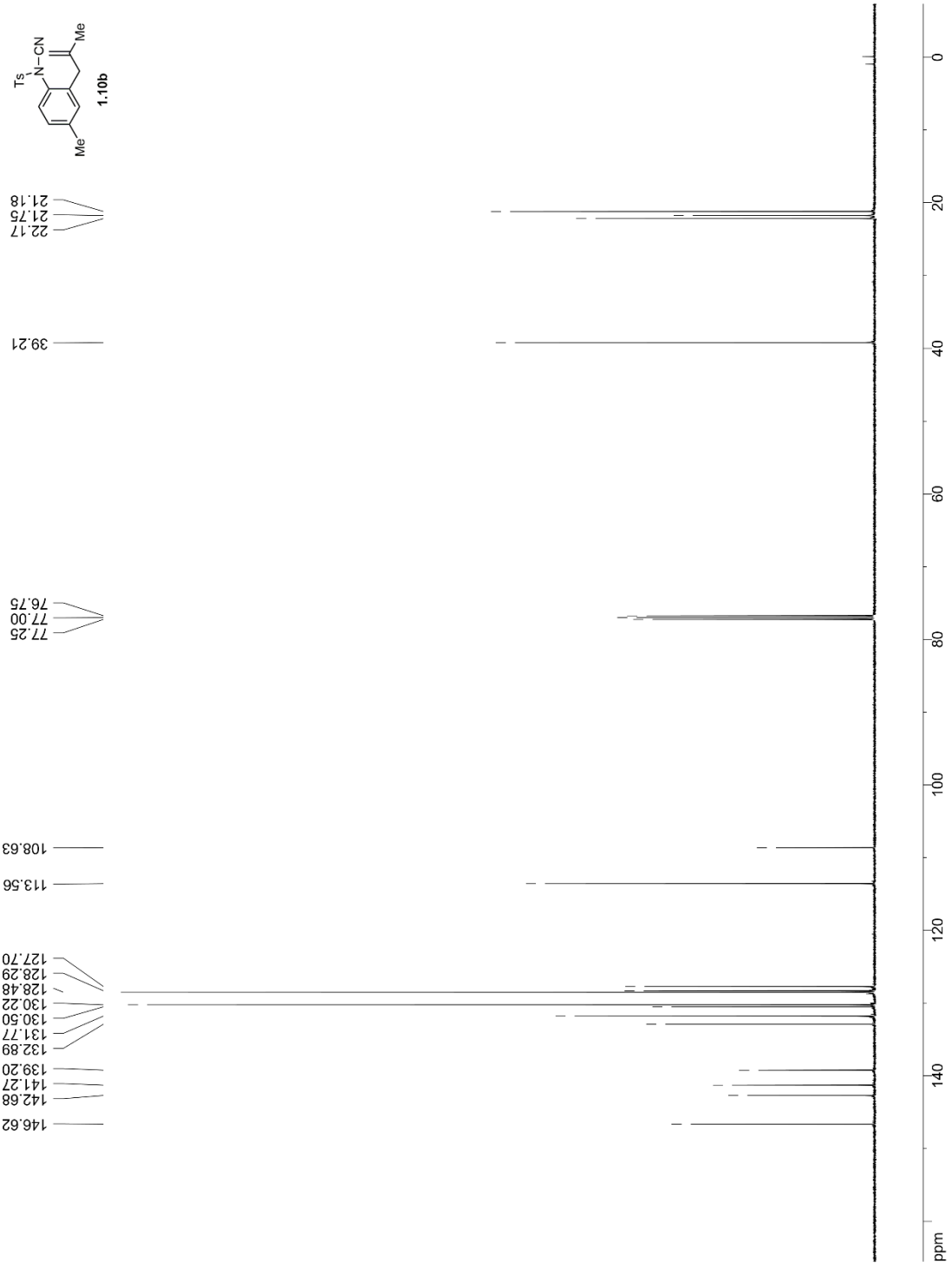
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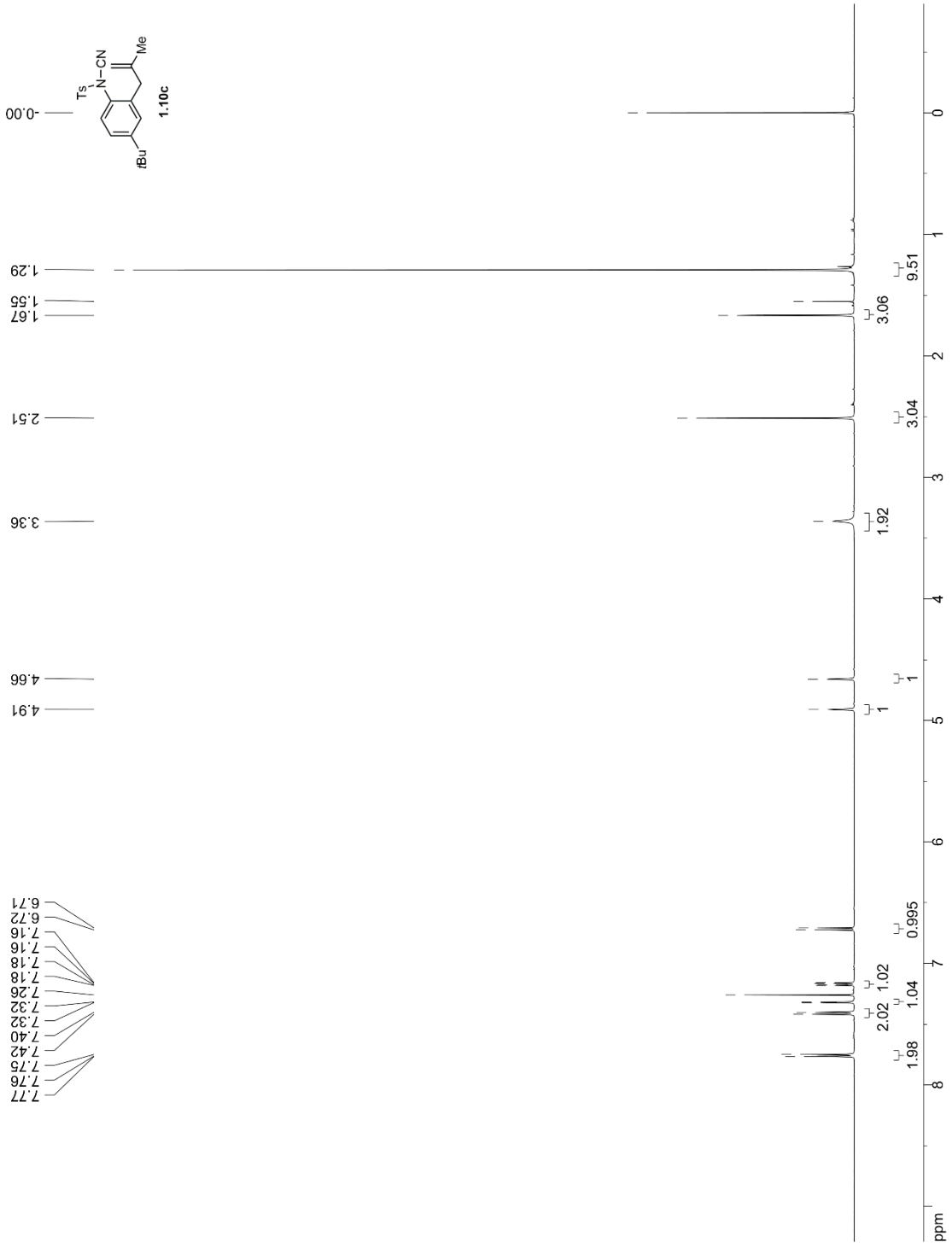
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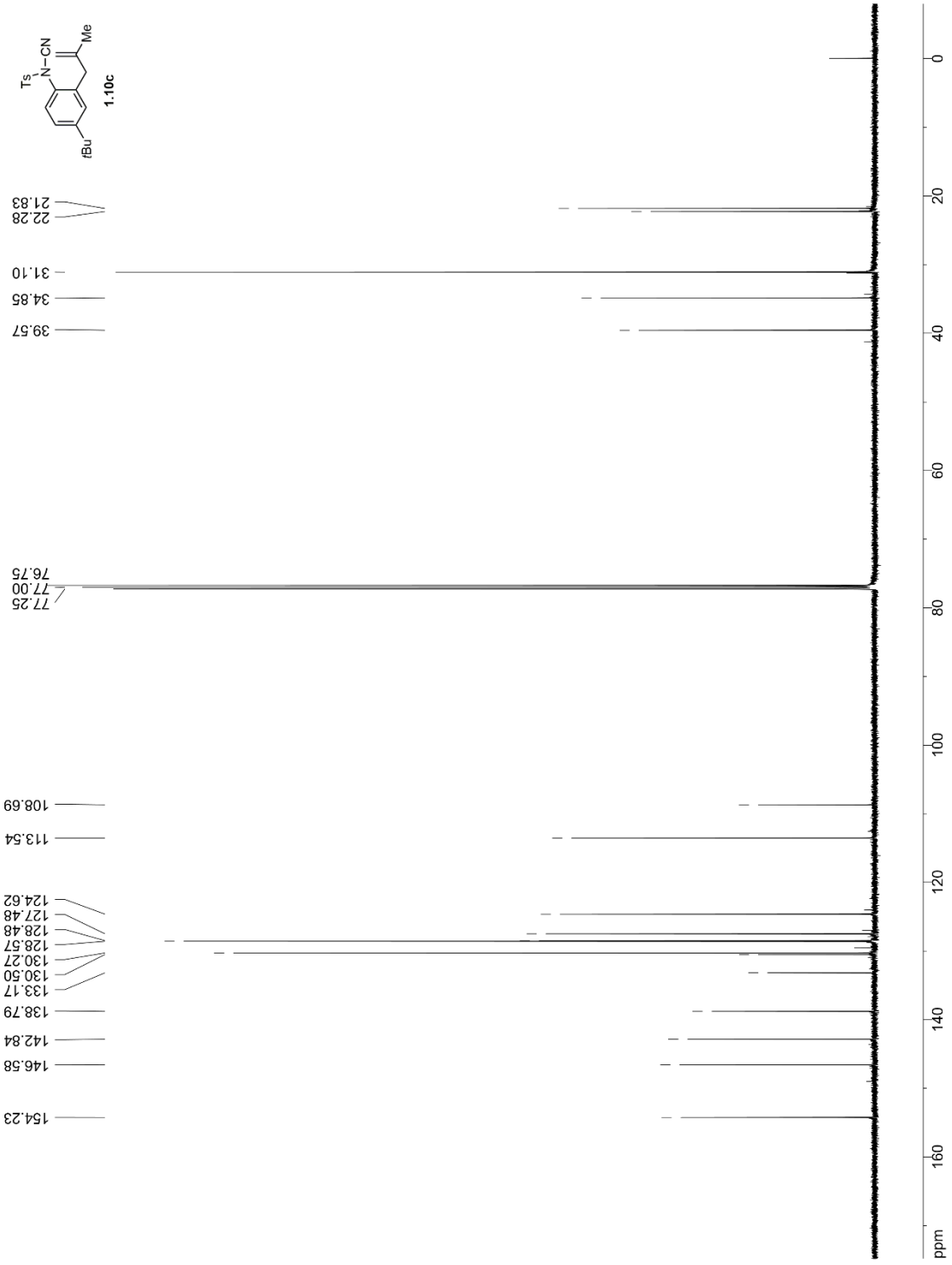
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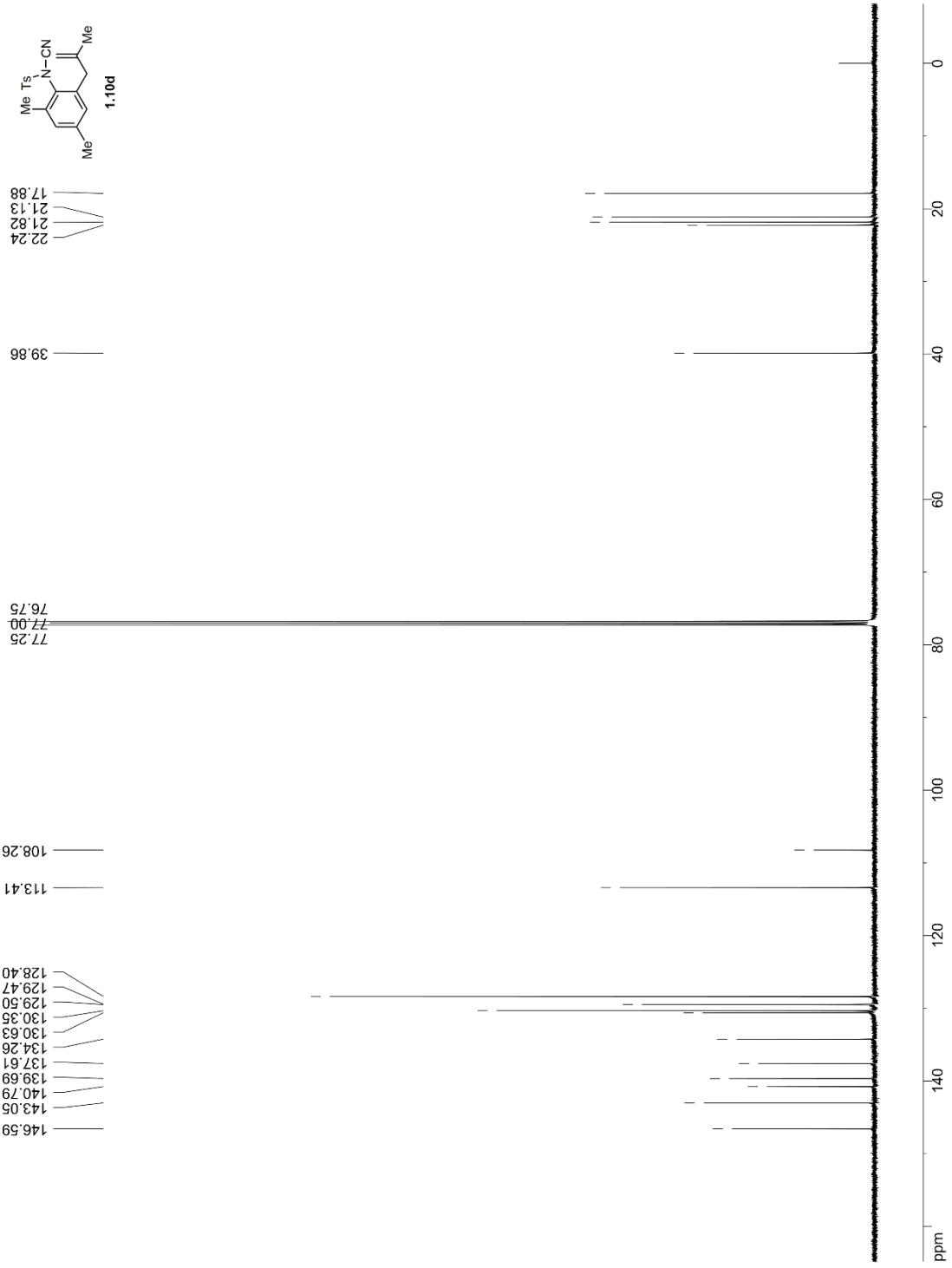
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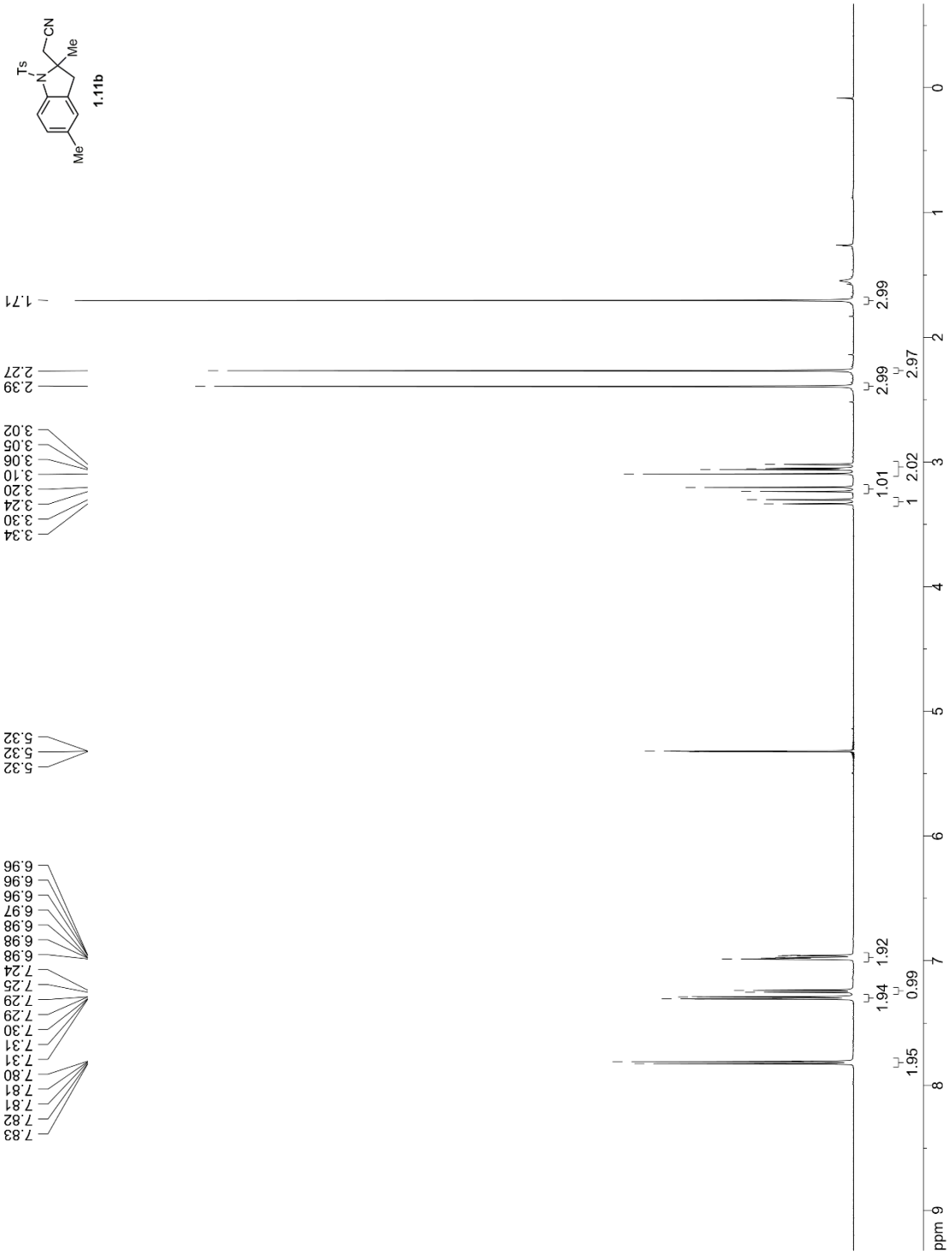
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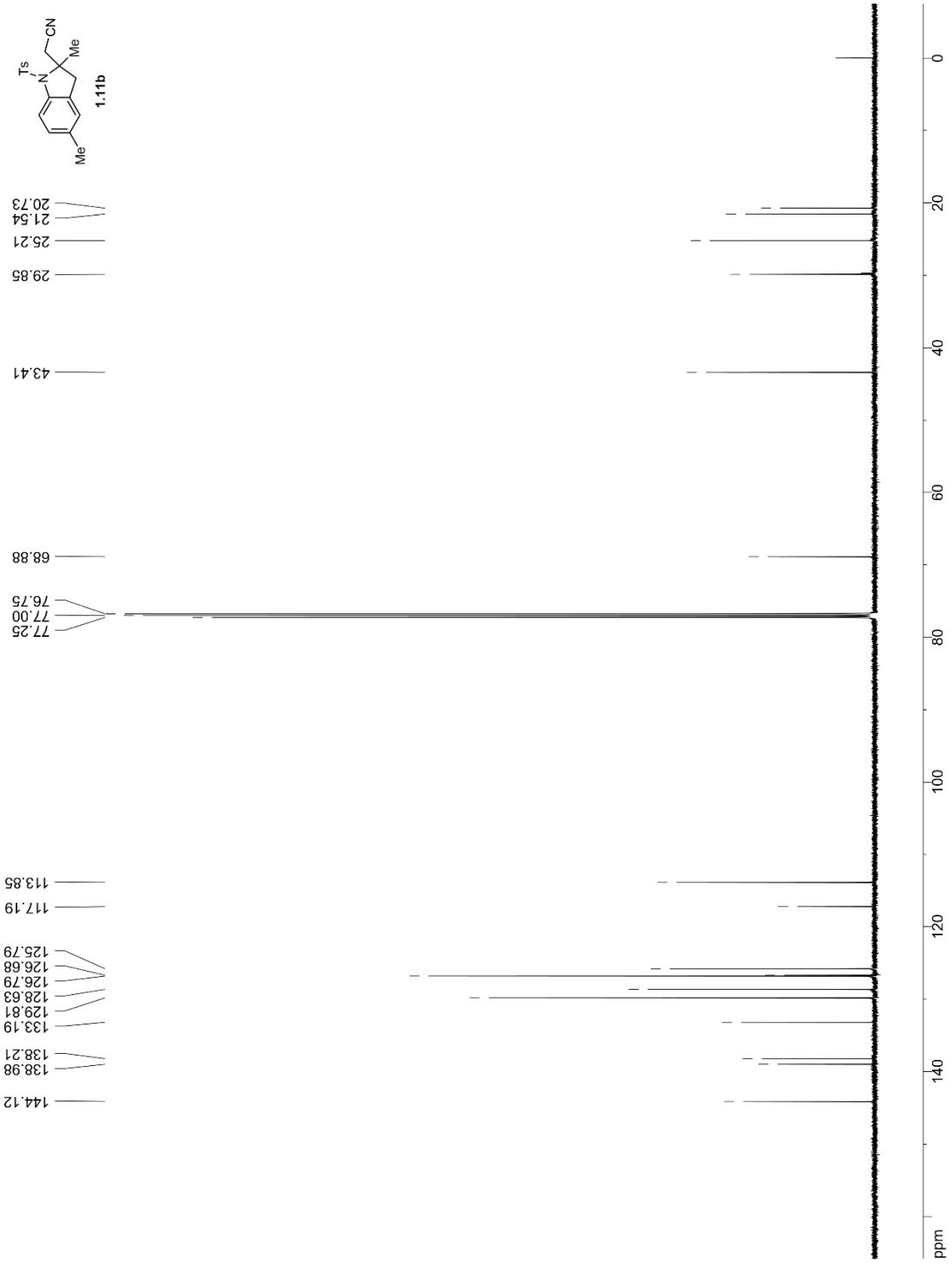
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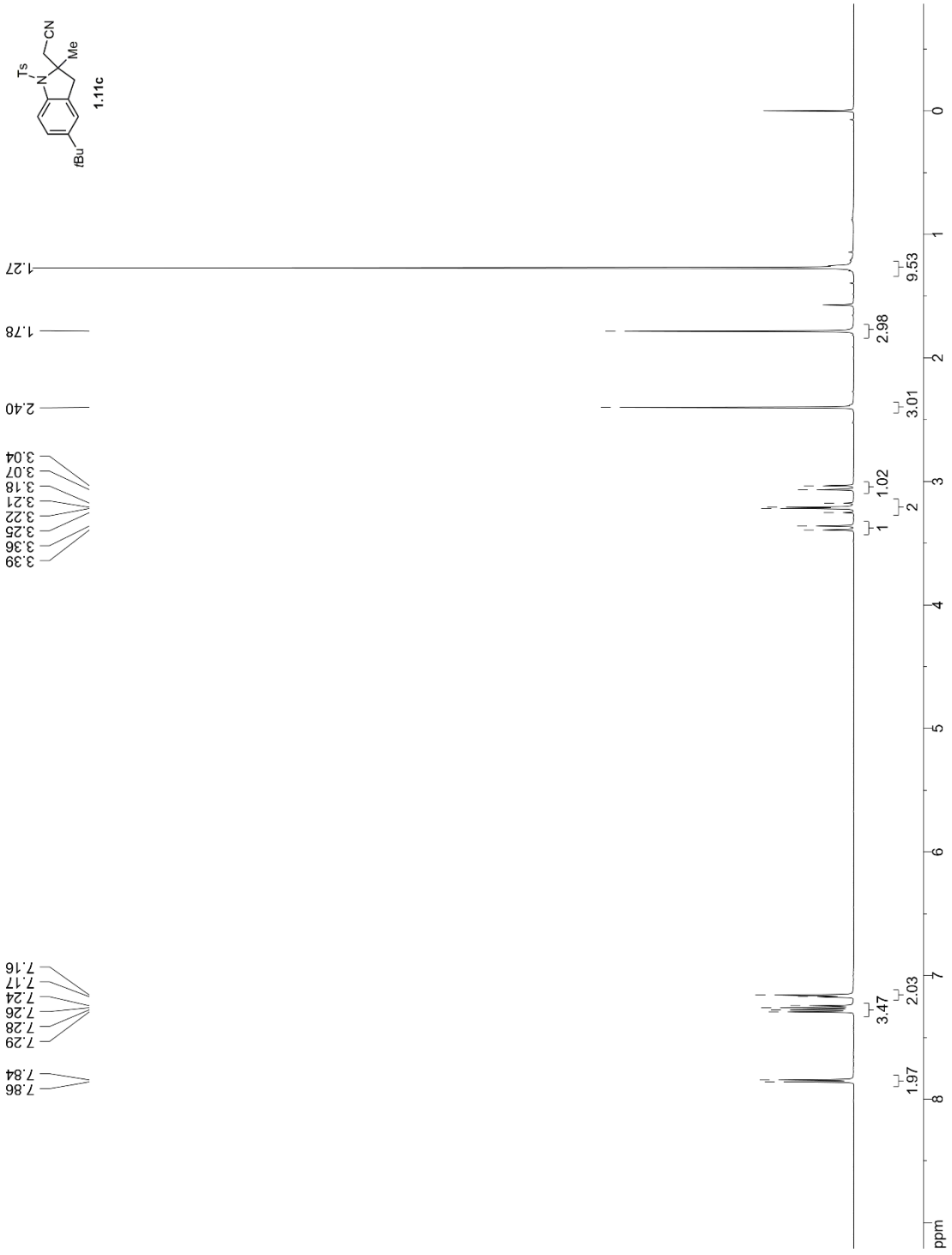
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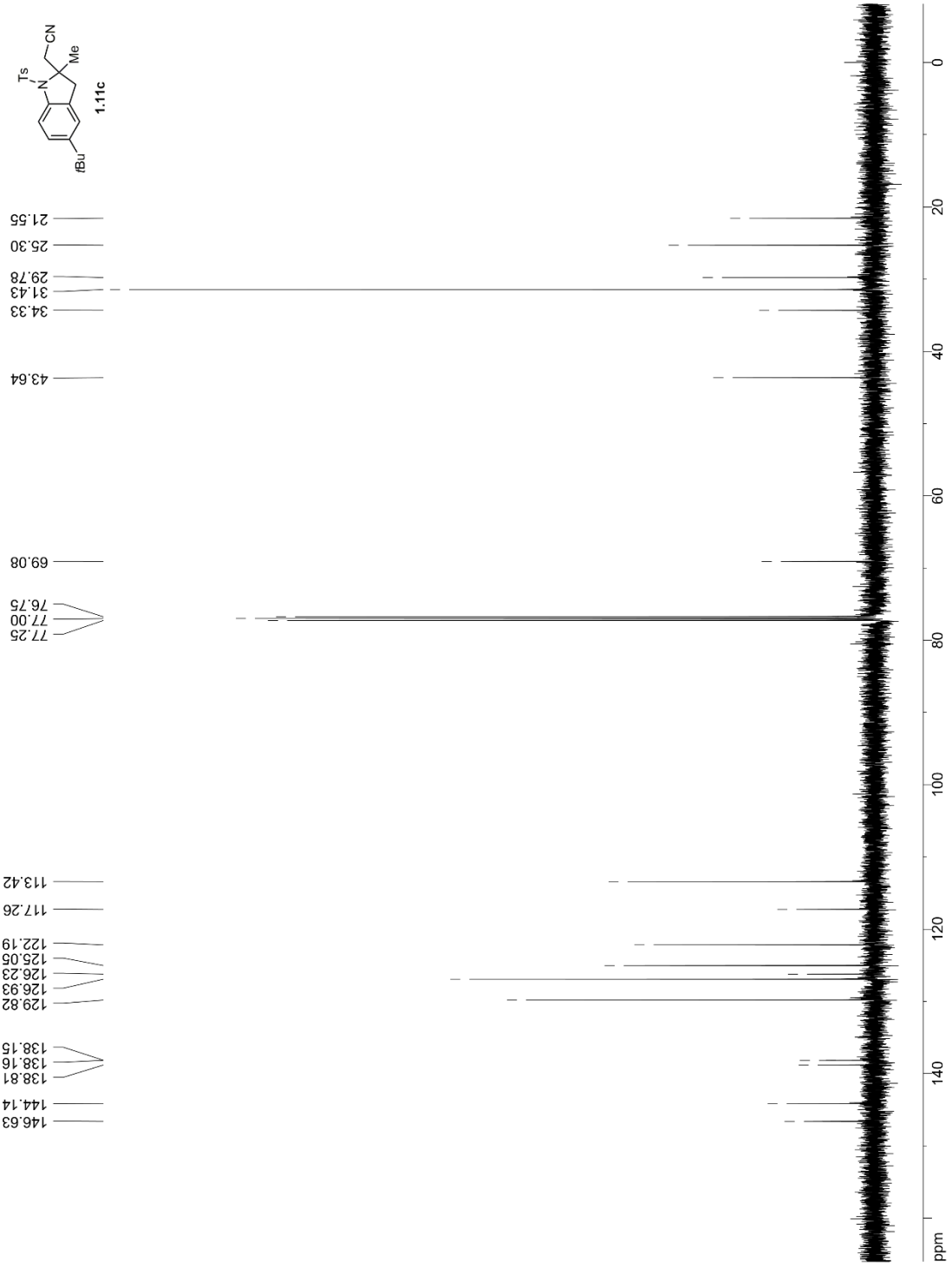
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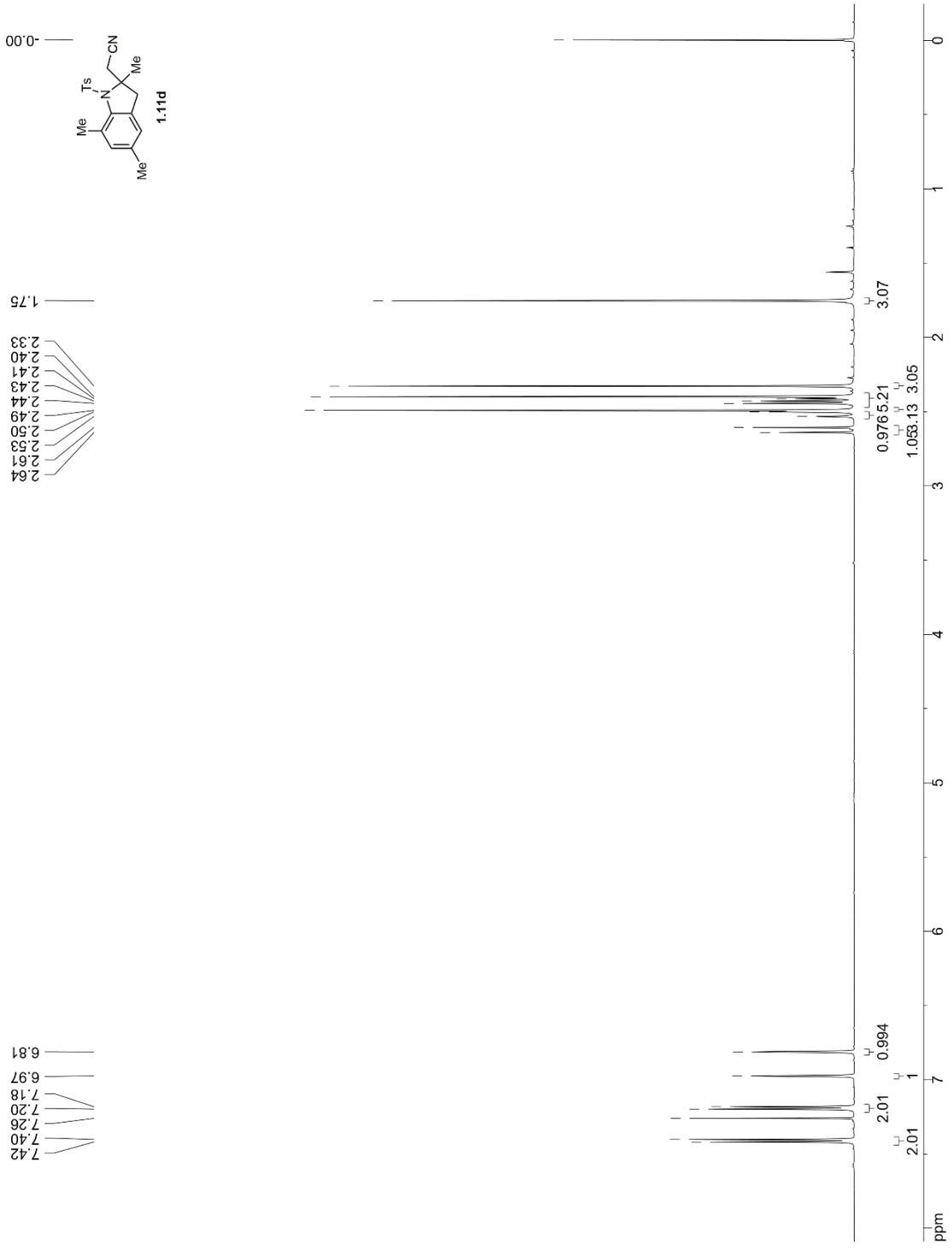
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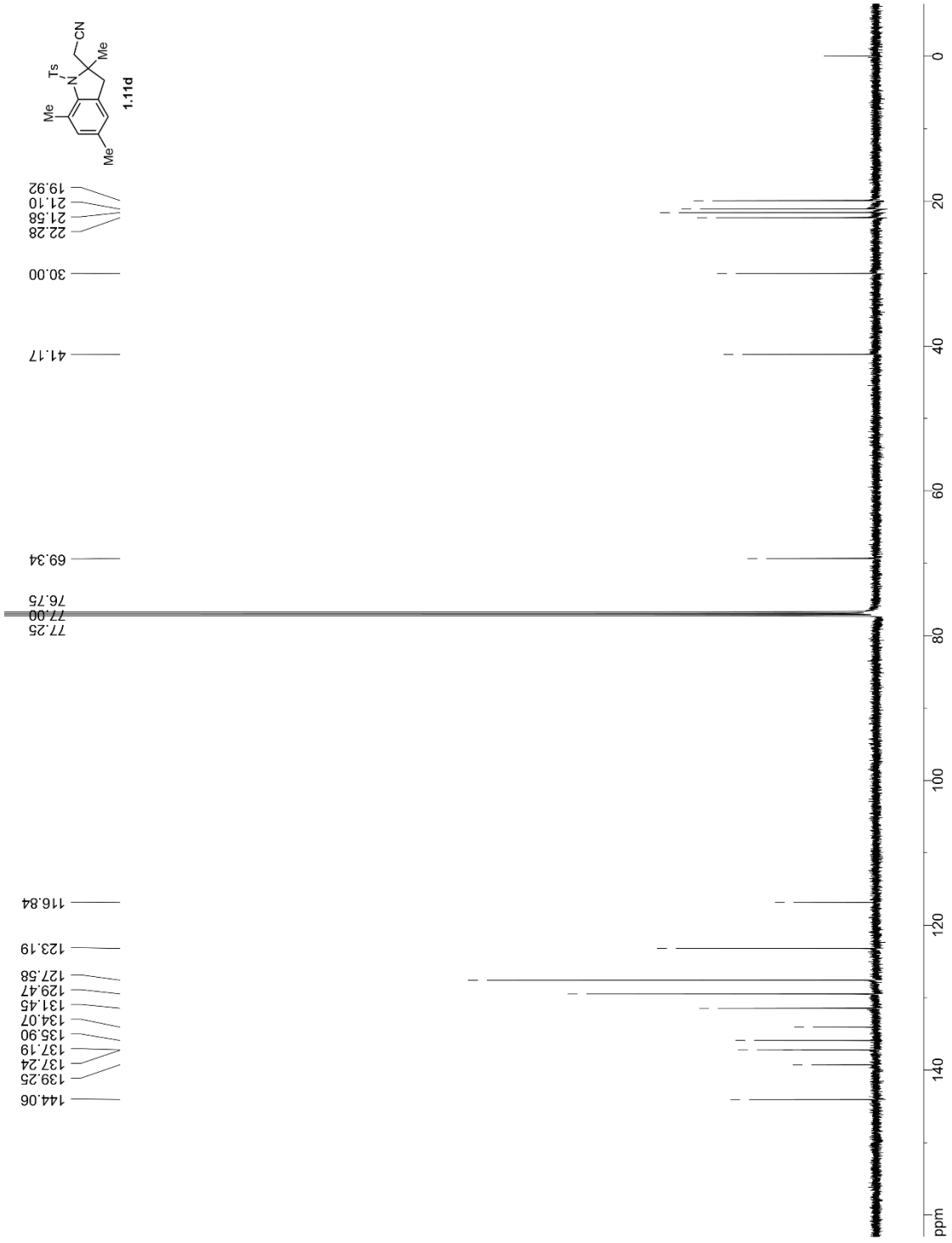
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21.58
22.28
30.00
41.17
69.34
76.75
77.00
77.25
116.84
123.19
127.58
129.47
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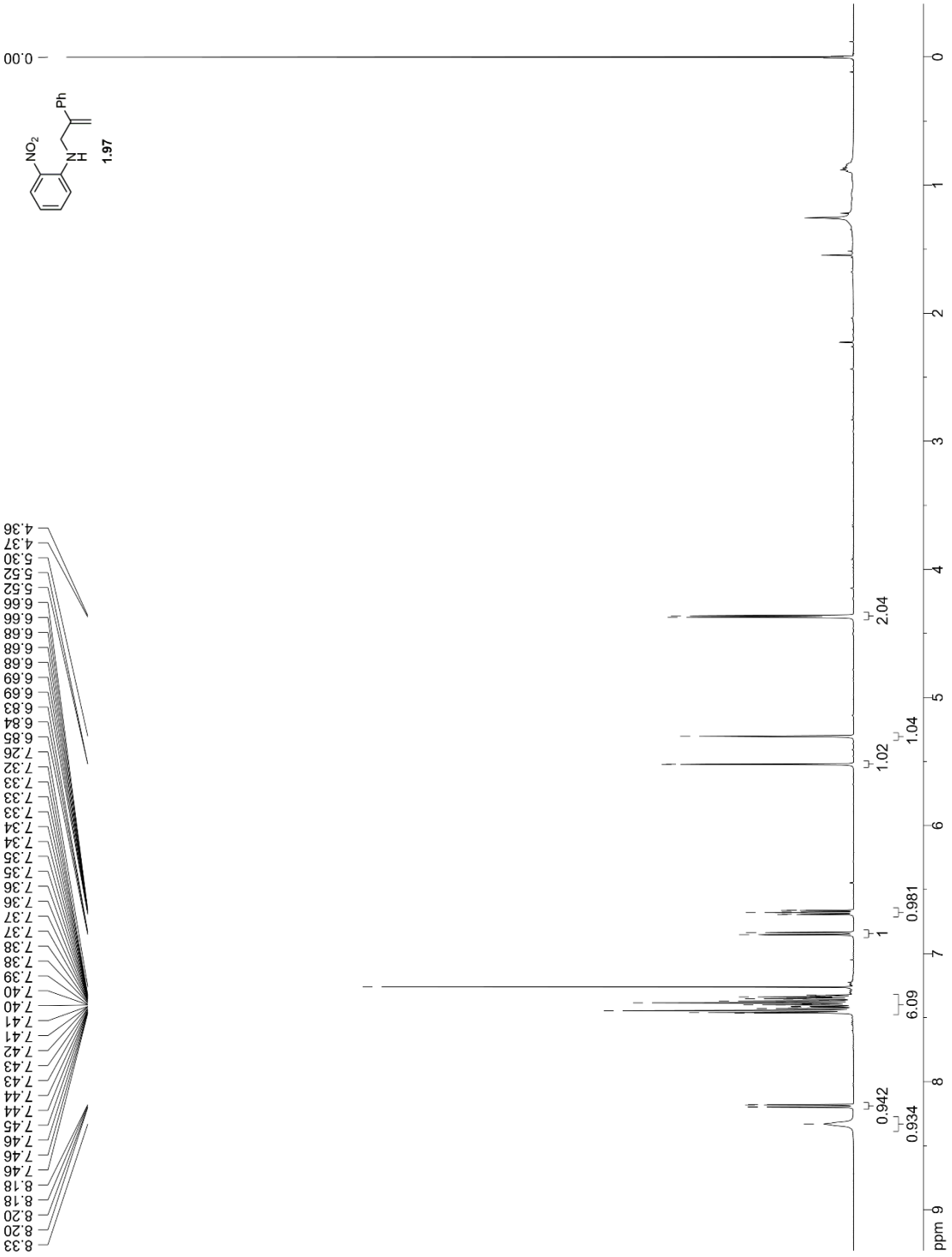
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7.46
7.45
7.44
7.44
7.43
7.43
7.42
7.41
7.41
7.40
7.40
7.39
7.38
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.33
7.33
7.33
7.32
7.26
6.85
6.84
6.83
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6.69
6.68
6.68
6.68
6.66
6.66
5.52
5.52
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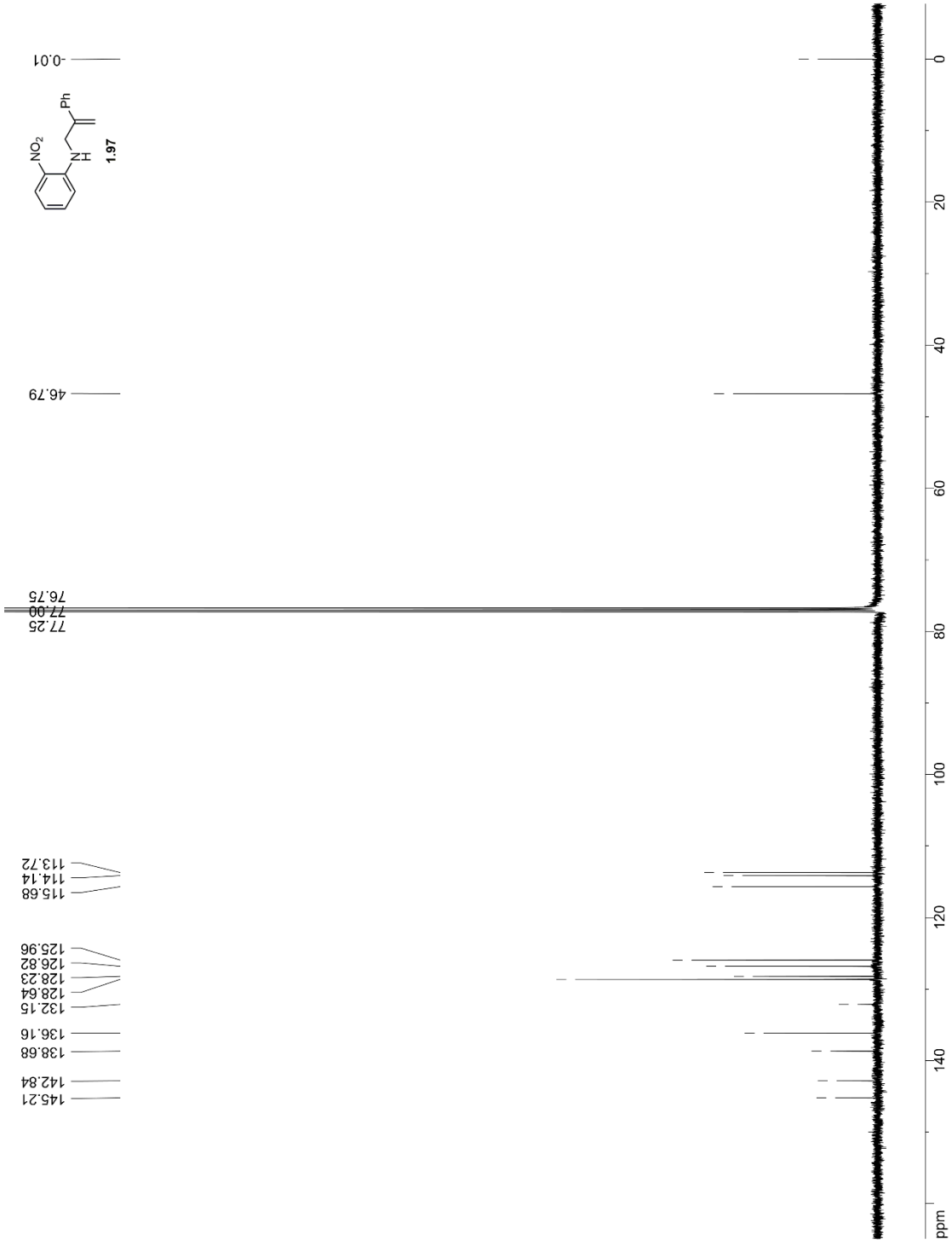
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115.68
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126.82
128.23
128.64
132.15
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138.68
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145.21
1.97
NO2
NH
Ph
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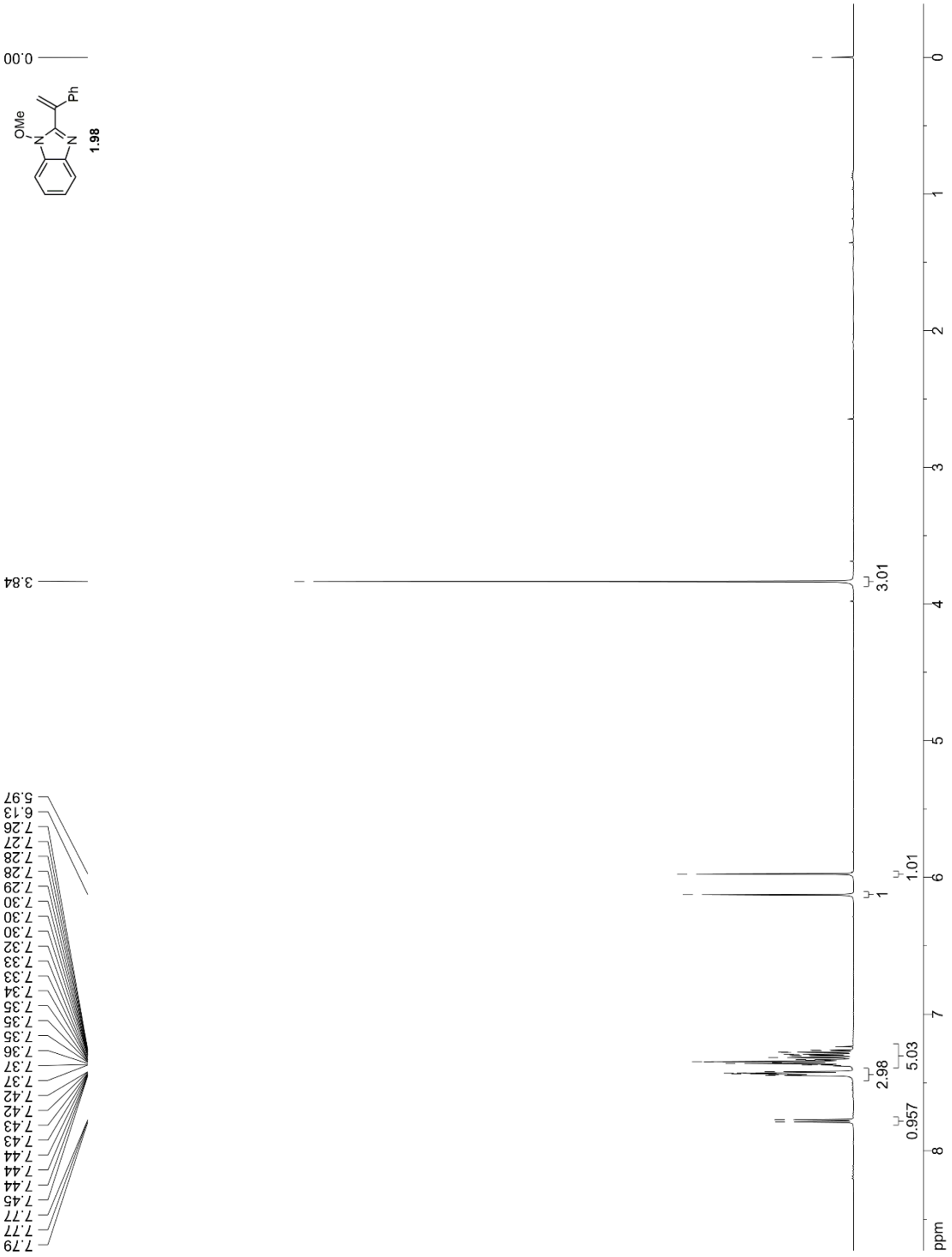
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7.42
7.37
7.37
7.36
7.35
7.35
7.35
7.34
7.33
7.33
7.32
7.30
7.30
7.30
7.29
7.28
7.28
7.27
7.26
6.13
5.97
3.01
1
1.01
2.98
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ppm
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3
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5
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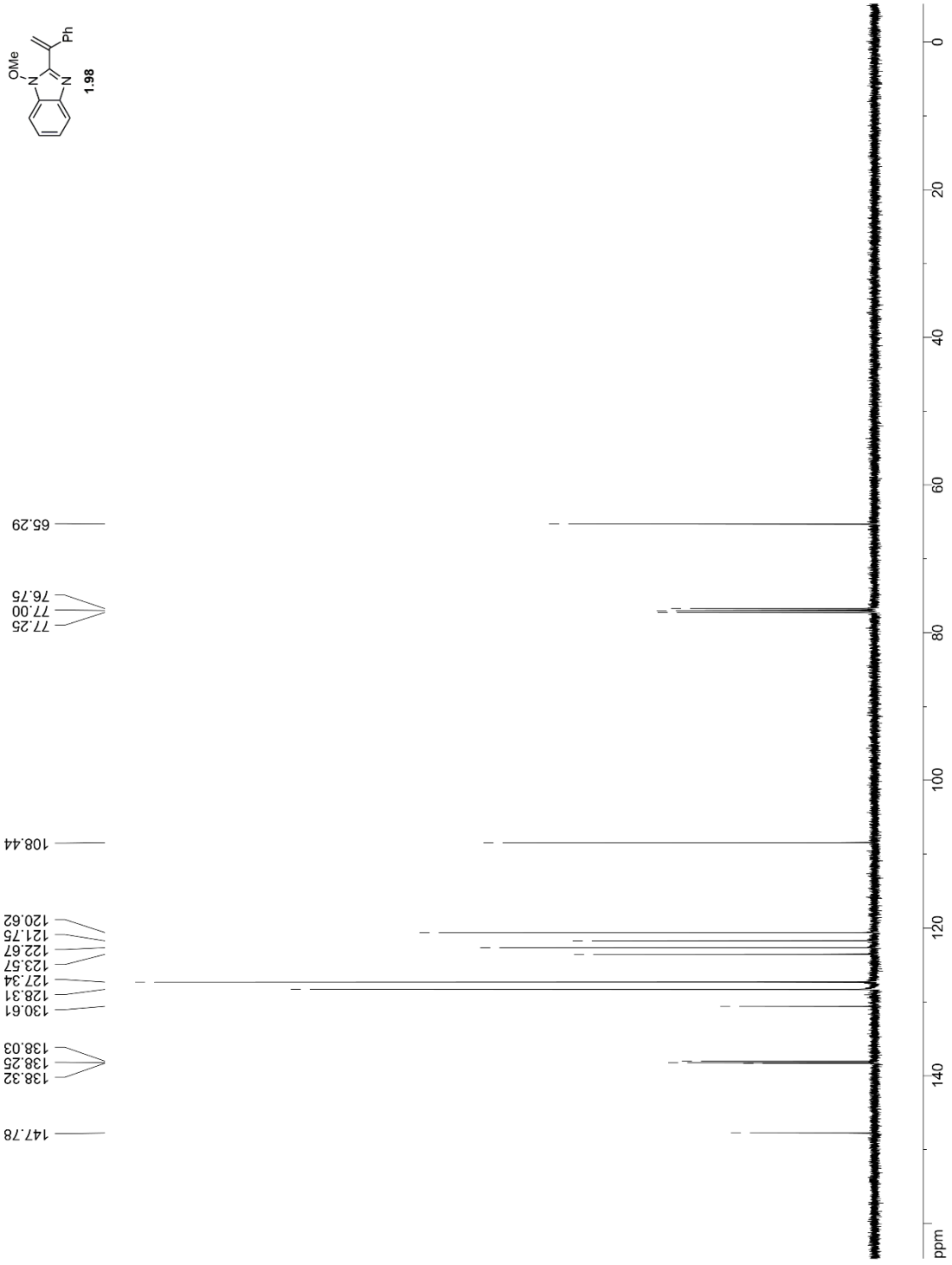
7
8
OMe
Ph
N
N
1.98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121.75
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123.57
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128.31
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138.03
138.25
138.32
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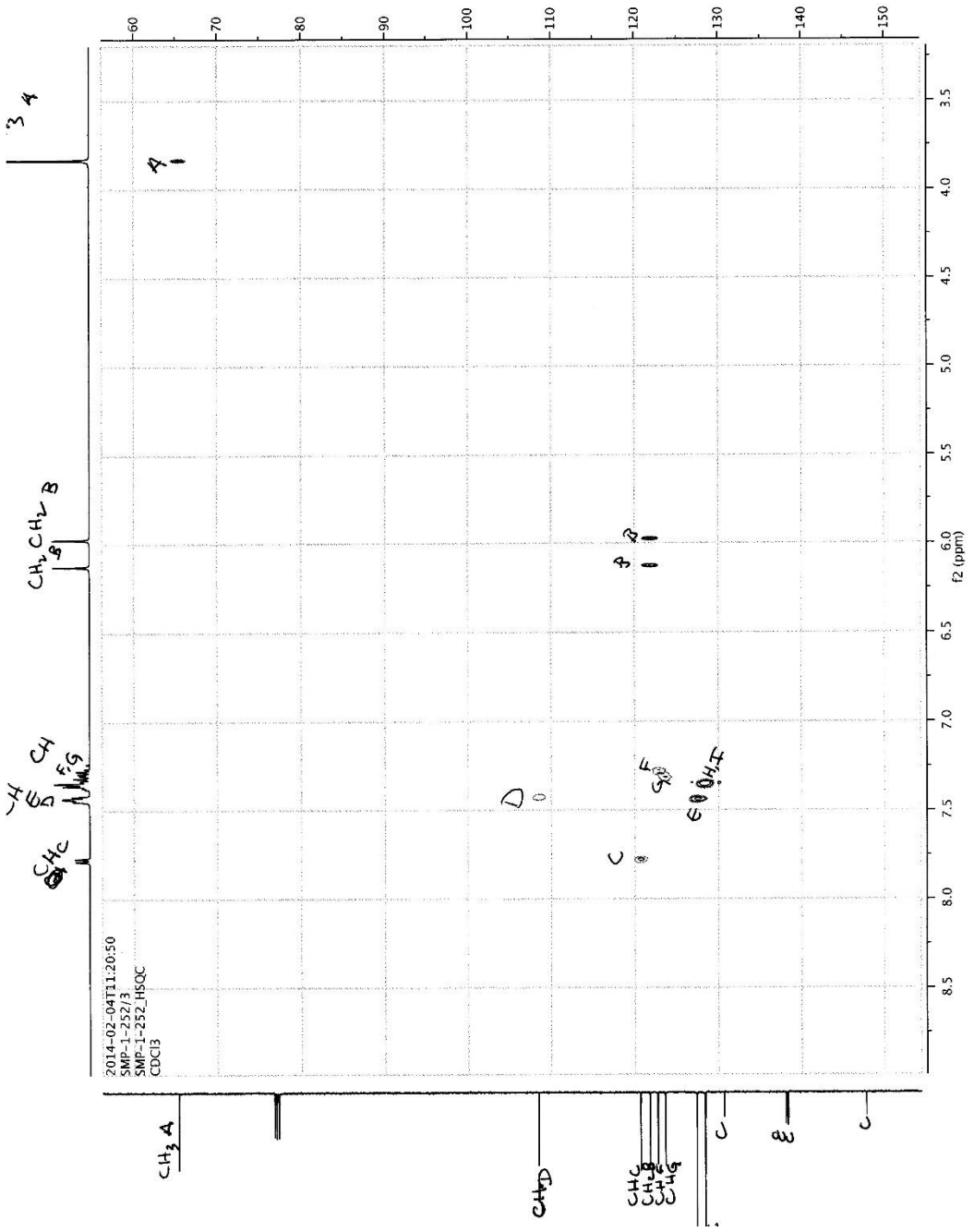
100
120
140
ppm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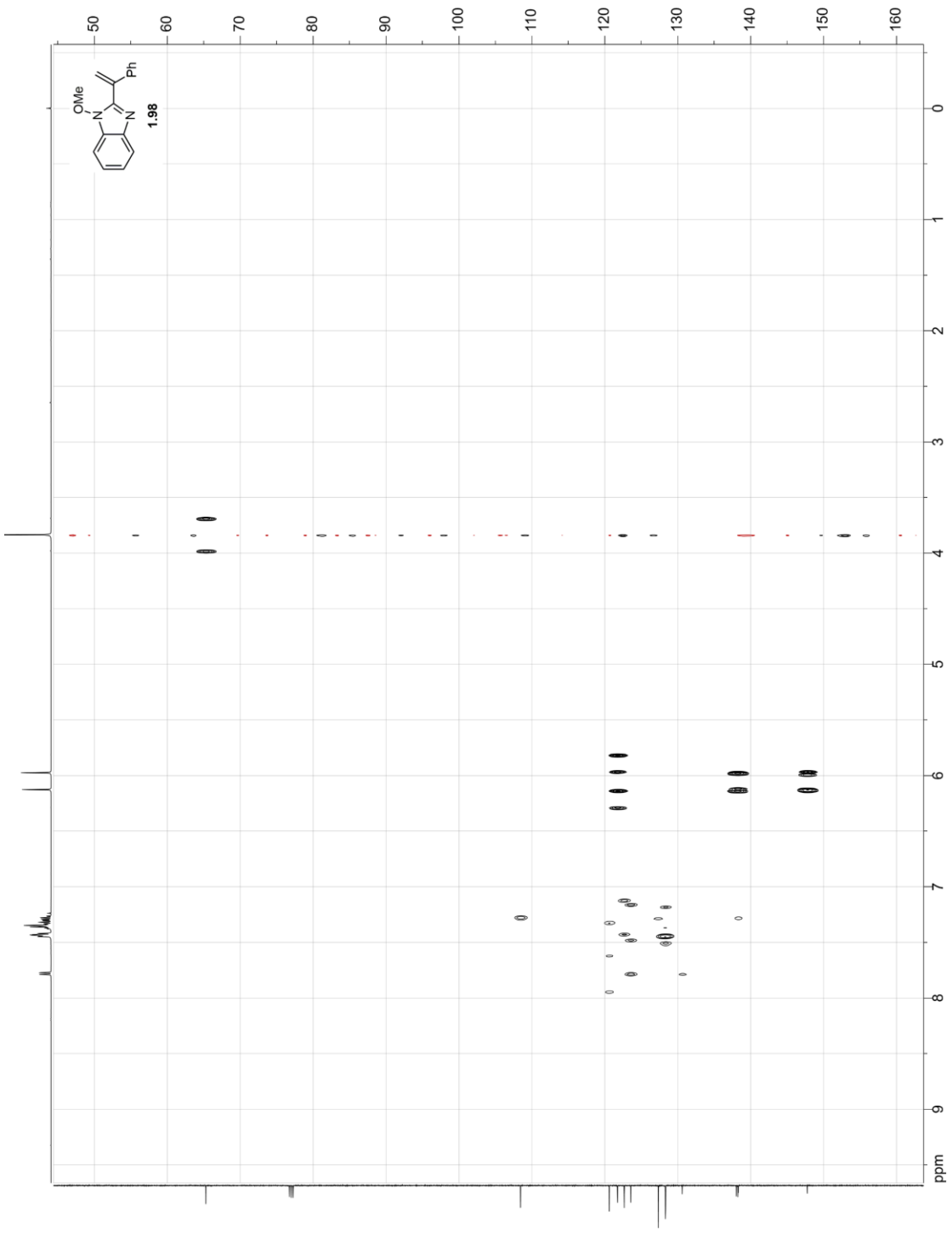
OMe
Ph
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N
1.98
50
60
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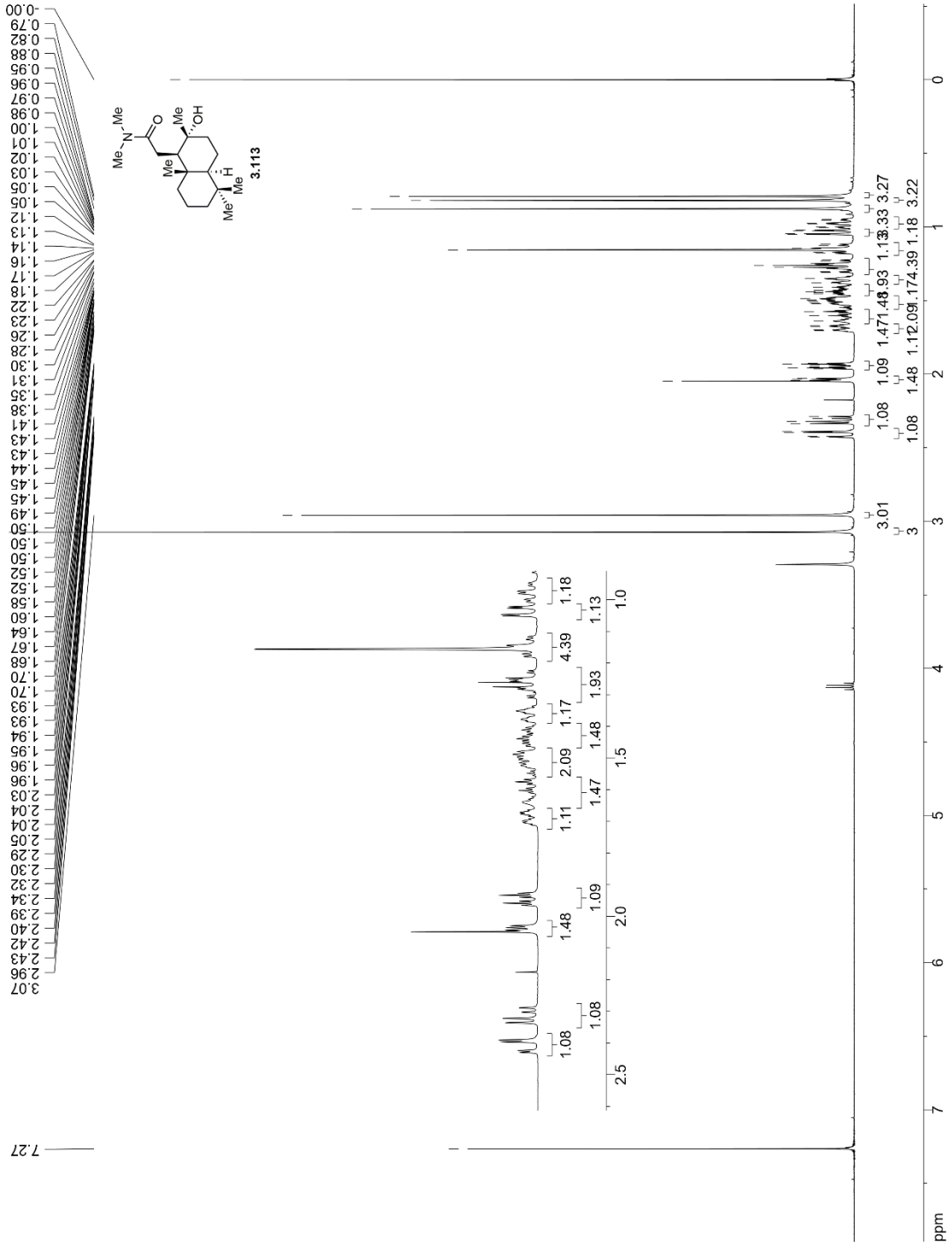
140
150
160
0
1
2
3
4
5
6
7
8
9
ppm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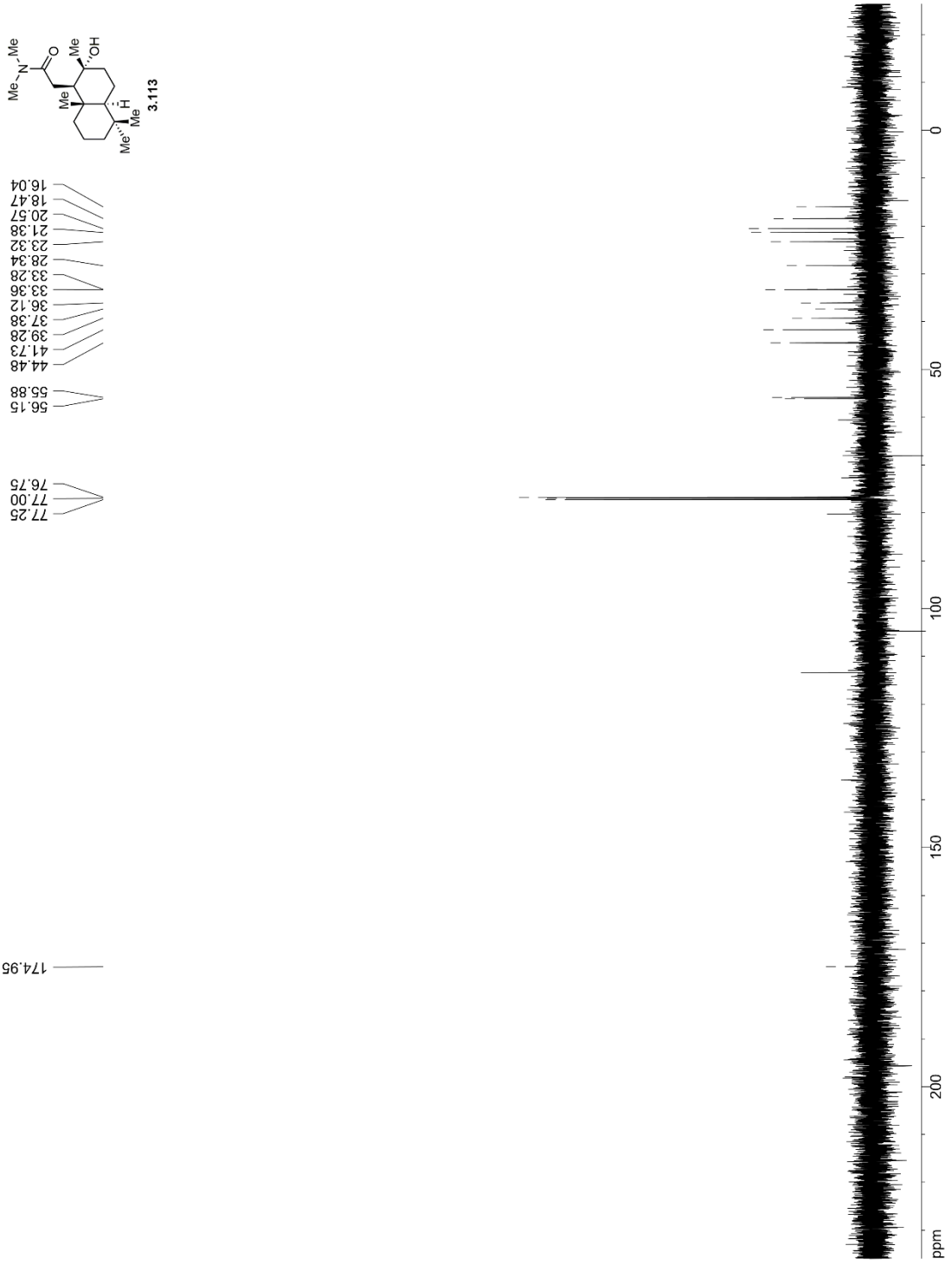
ppm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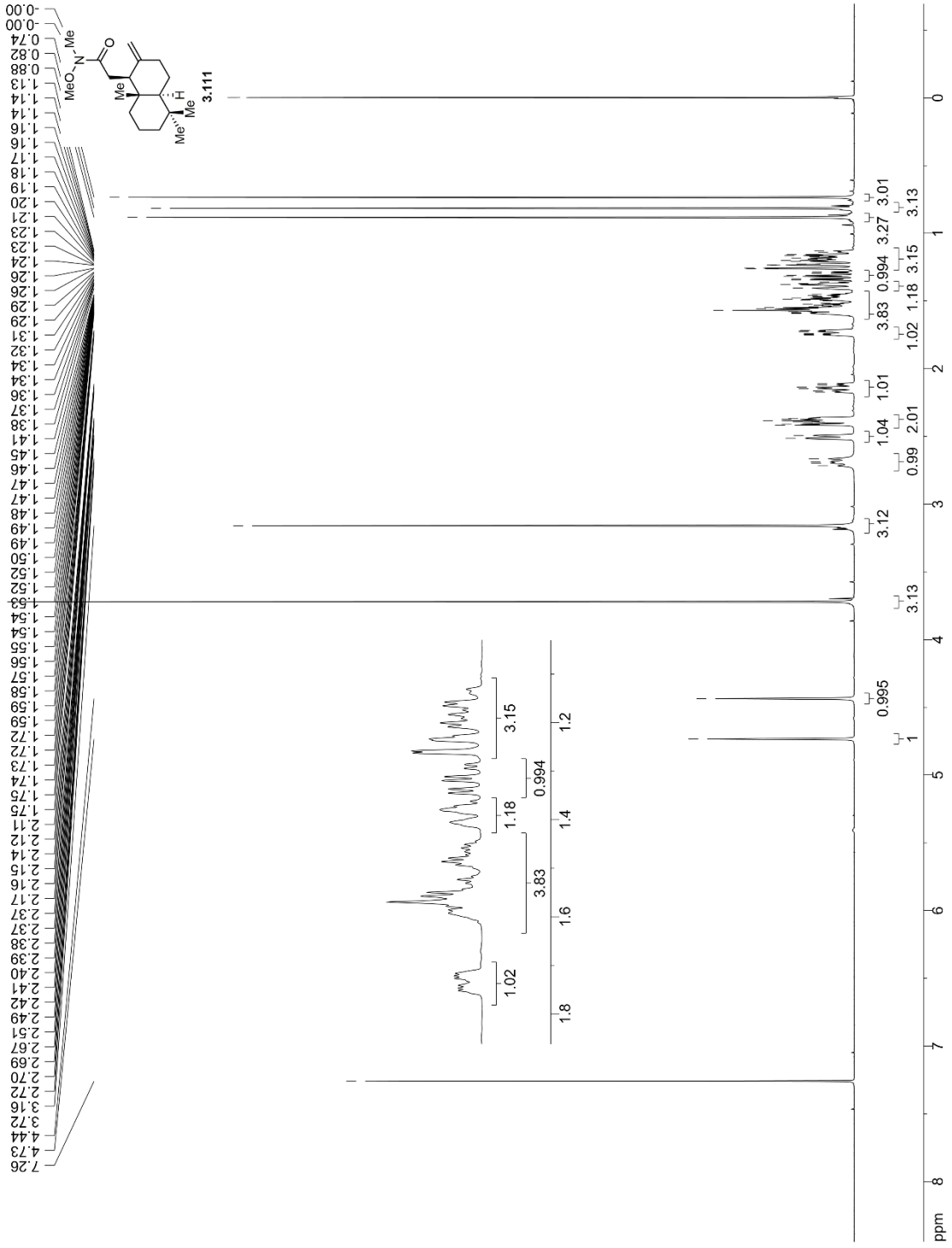
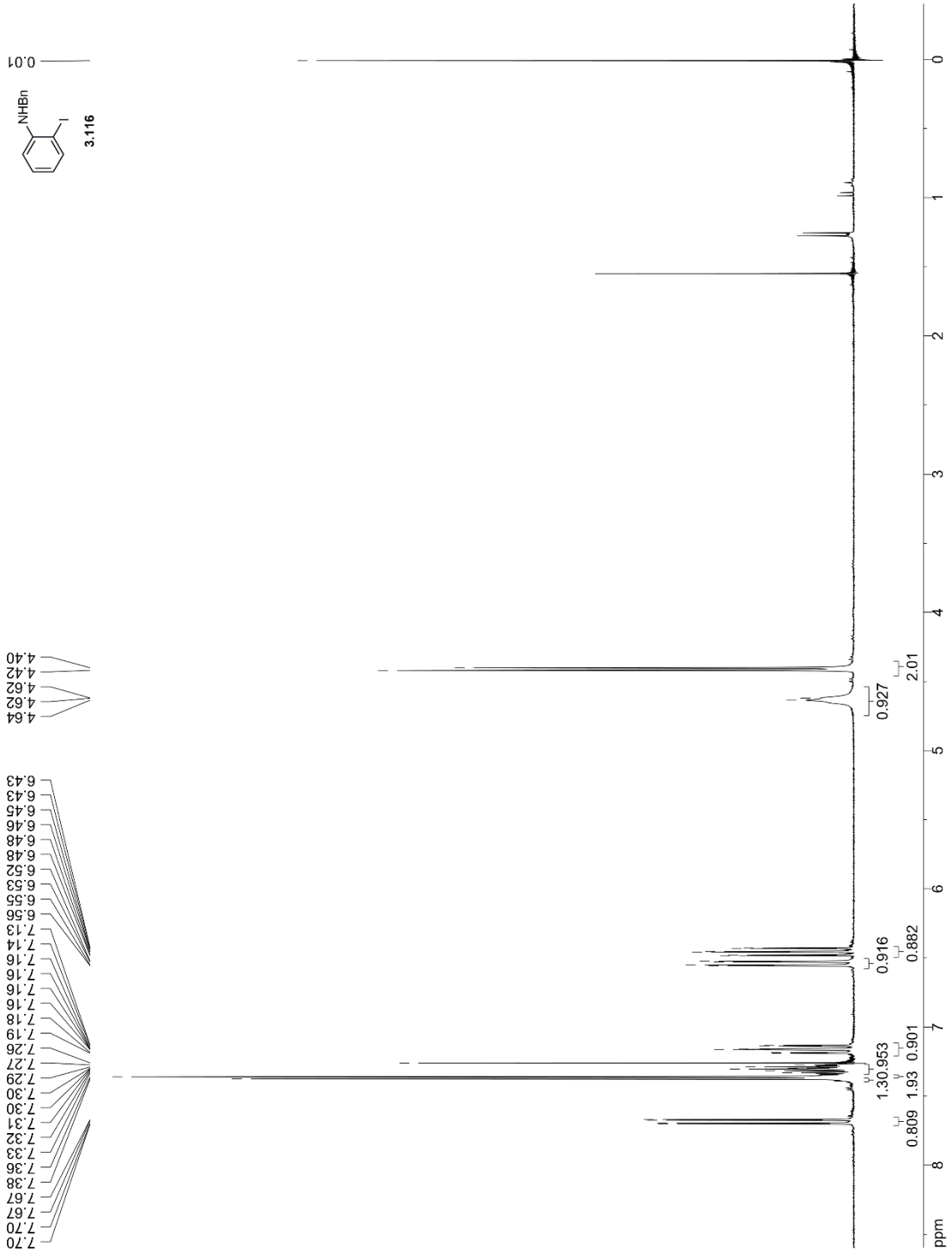
N
Me
O
Me
OH
Me
H
Me
Me
3.113
16.04
18.47
20.57
21.38
23.32
28.34
33.28
33.36
36.12
37.38
39.28
41.73
44.48
55.88
56.15
76.75
77.00
77.25
174.95
0
50
100
150
200
ppm


MeO
N
Me
O
Me
Me
H
Me
3.111
ppm


NHBn
I
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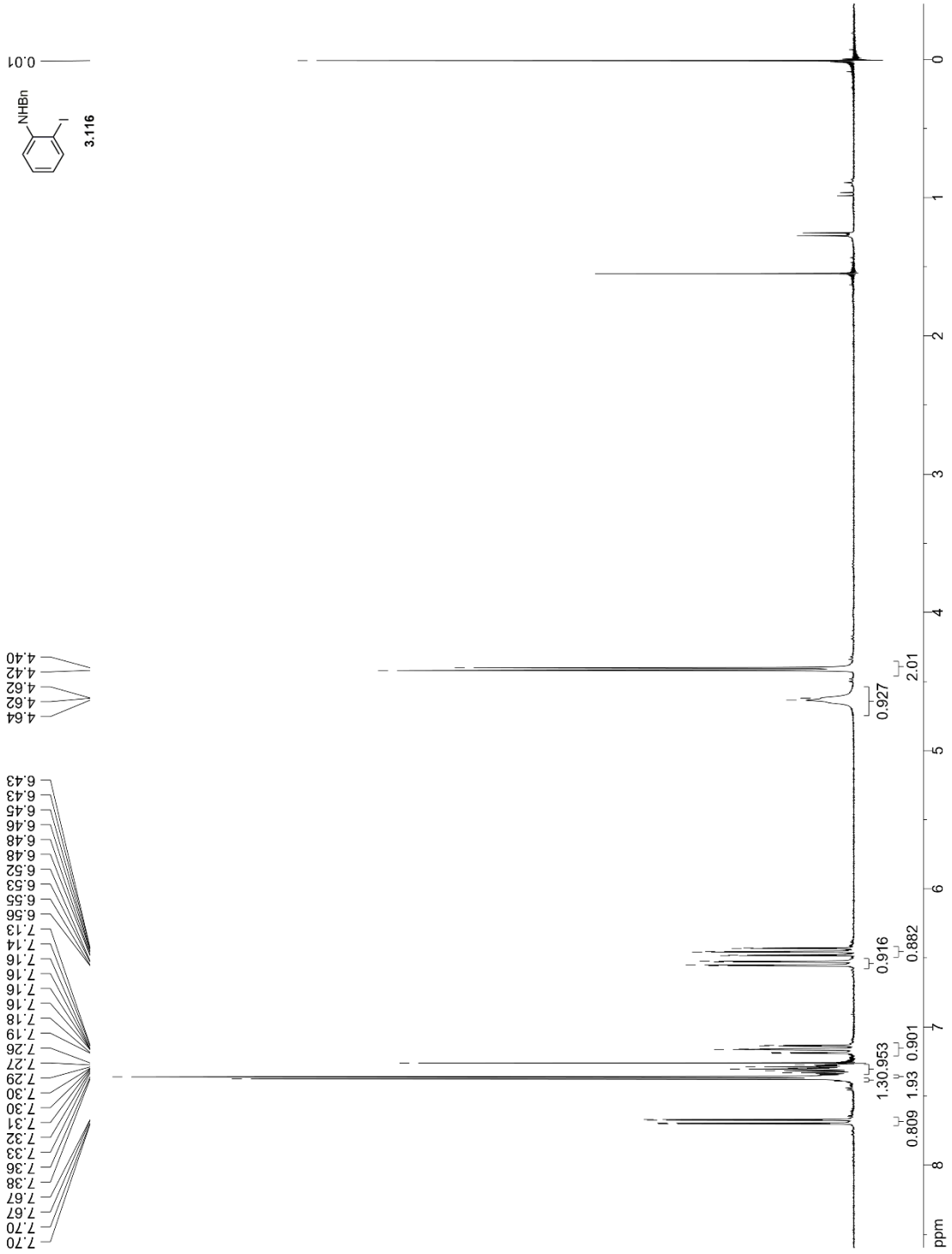
4.62
4.62
4.42
4.40
6.43
6.43
6.45
6.46
6.48
6.48
6.52
6.53
6.55
6.56
7.13
7.14
7.16
7.16
7.16
7.16
7.18
7.19
7.26
7.27
7.29
7.30
7.30
7.31
7.32
7.33
7.36
7.38
7.67
7.67
7.70
7.70
0.809
1.30
0.953
1.93
0.901
0.916
0.882
0.927
2.01
ppm


NHBn
I
3.116
0.01
4.64
4.62
4.62
4.42
4.40
6.43
6.43
6.45
6.46
6.48
6.48
6.52
6.53
6.55
6.56
7.13
7.14
7.16
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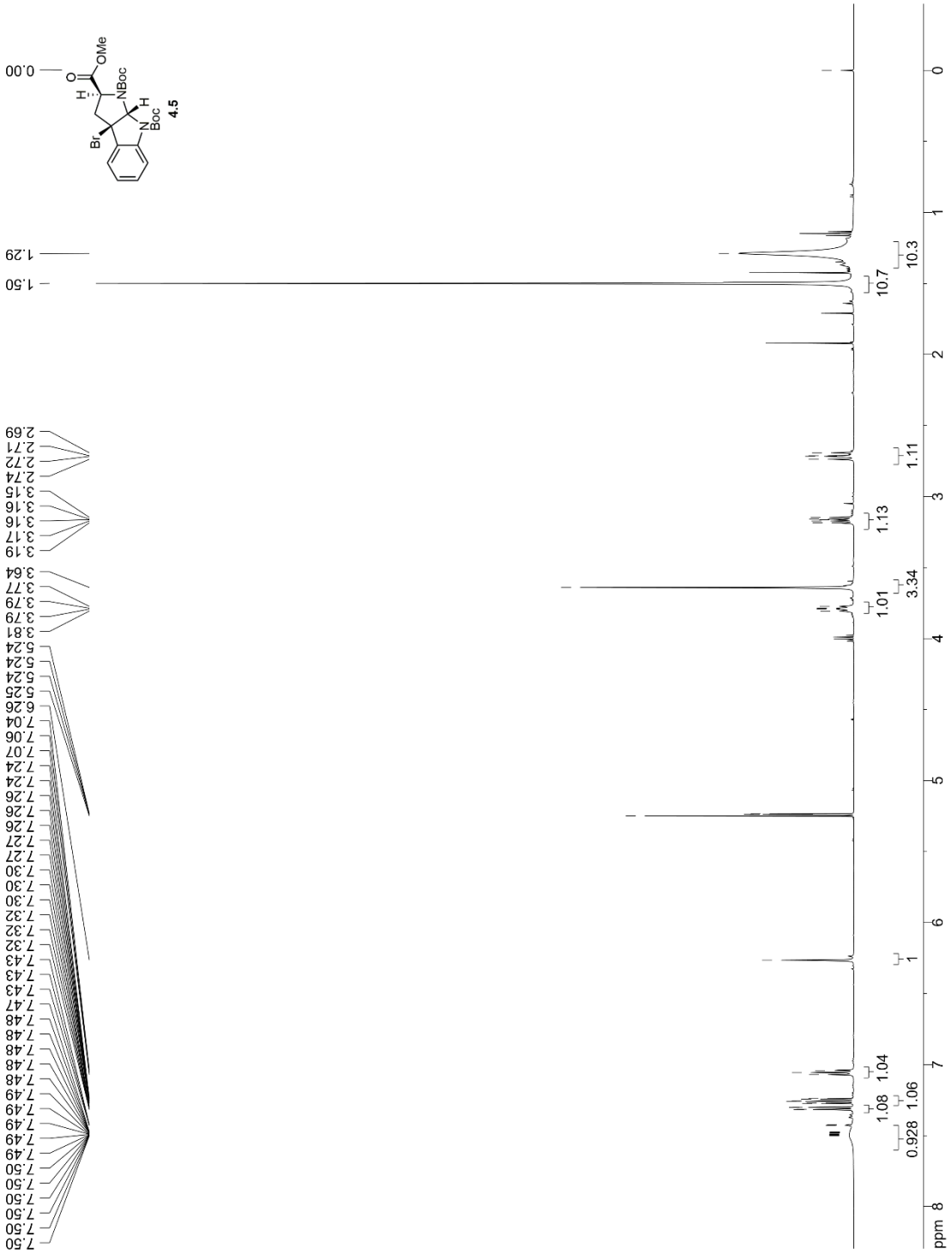
7.16
7.16
7.18
7.19
7.26
7.27
7.29
7.30
7.30
7.31
7.32
7.33
7.36
7.38
7.67
7.67
7.70
7.70
0.809
1.30
0.953
1.93
0.901
0.916
0.882
0.927
2.01
ppm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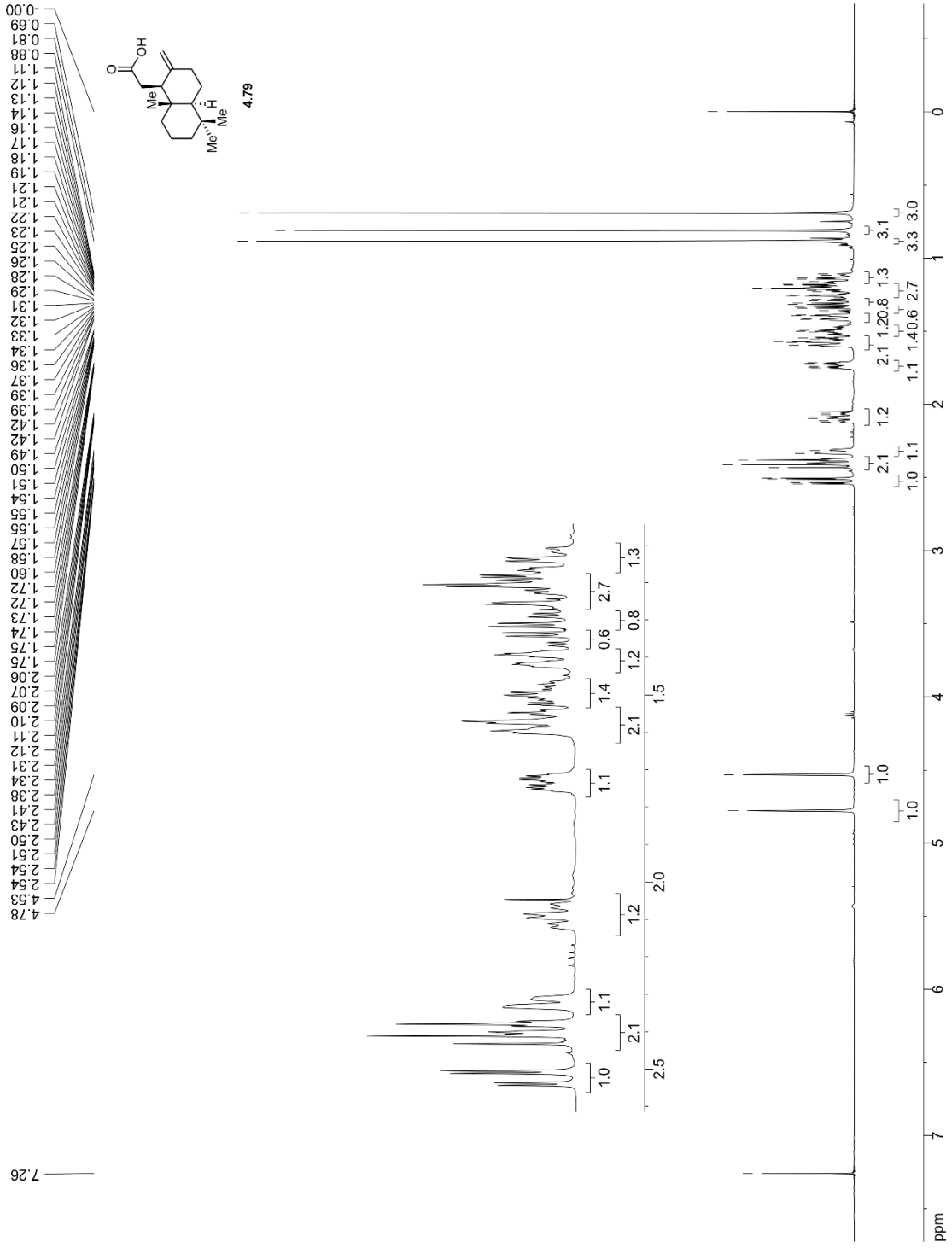
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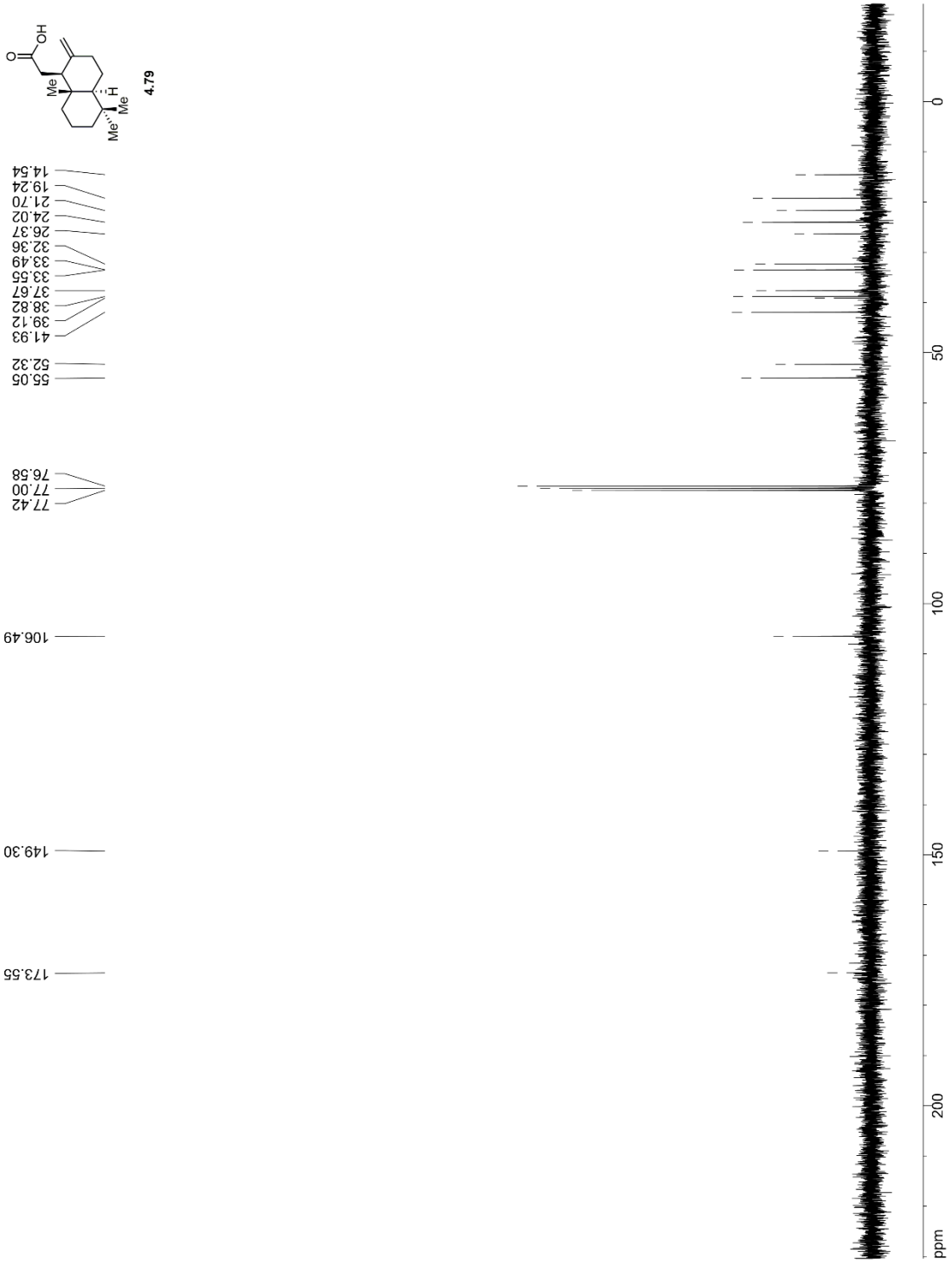
ppm


4.79
14.54
19.24
21.70
24.02
26.37
32.36
33.49
33.55
37.67
38.82
39.12
41.93
52.32
55.05
76.58
77.00
77.42
106.49
149.30
173.55
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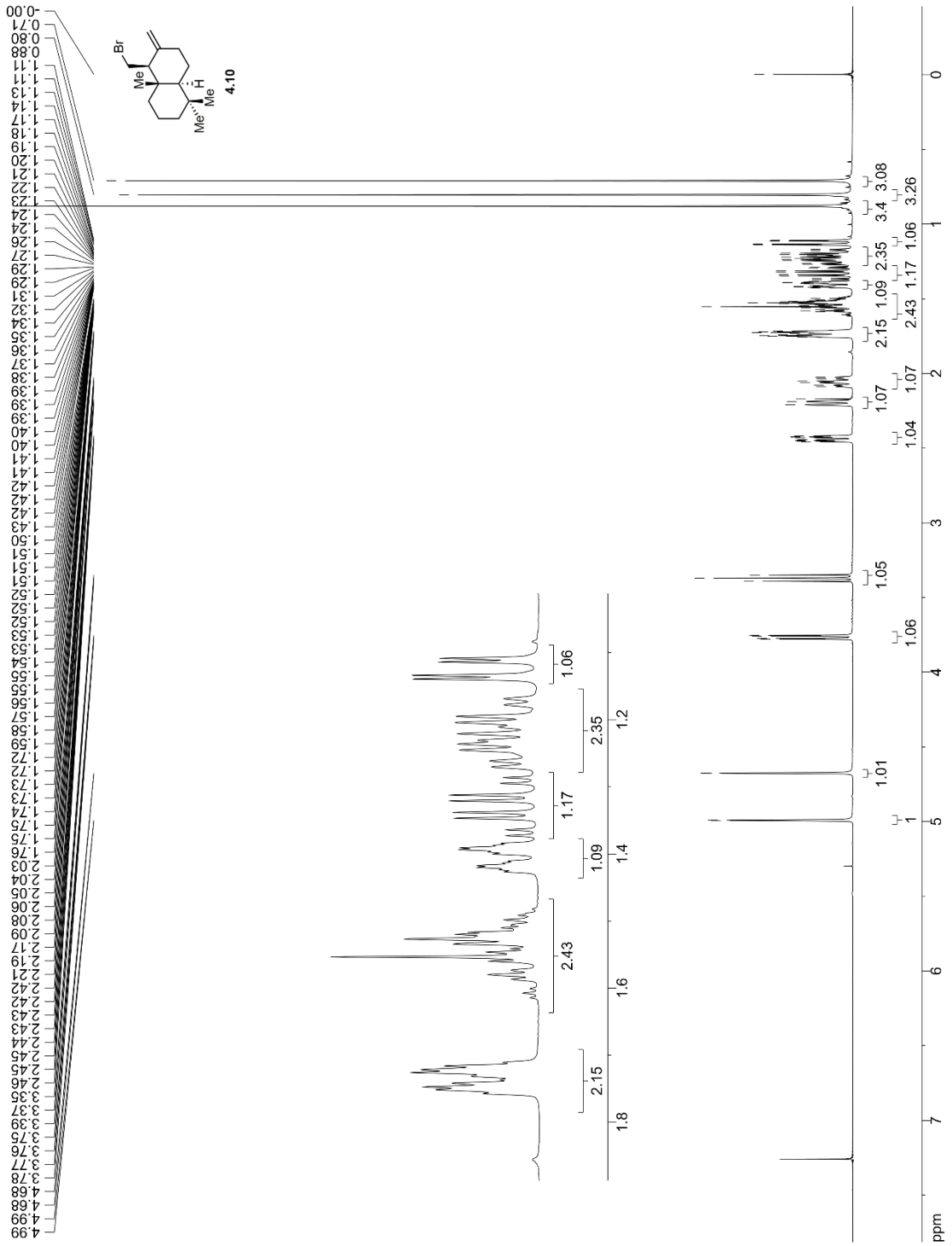
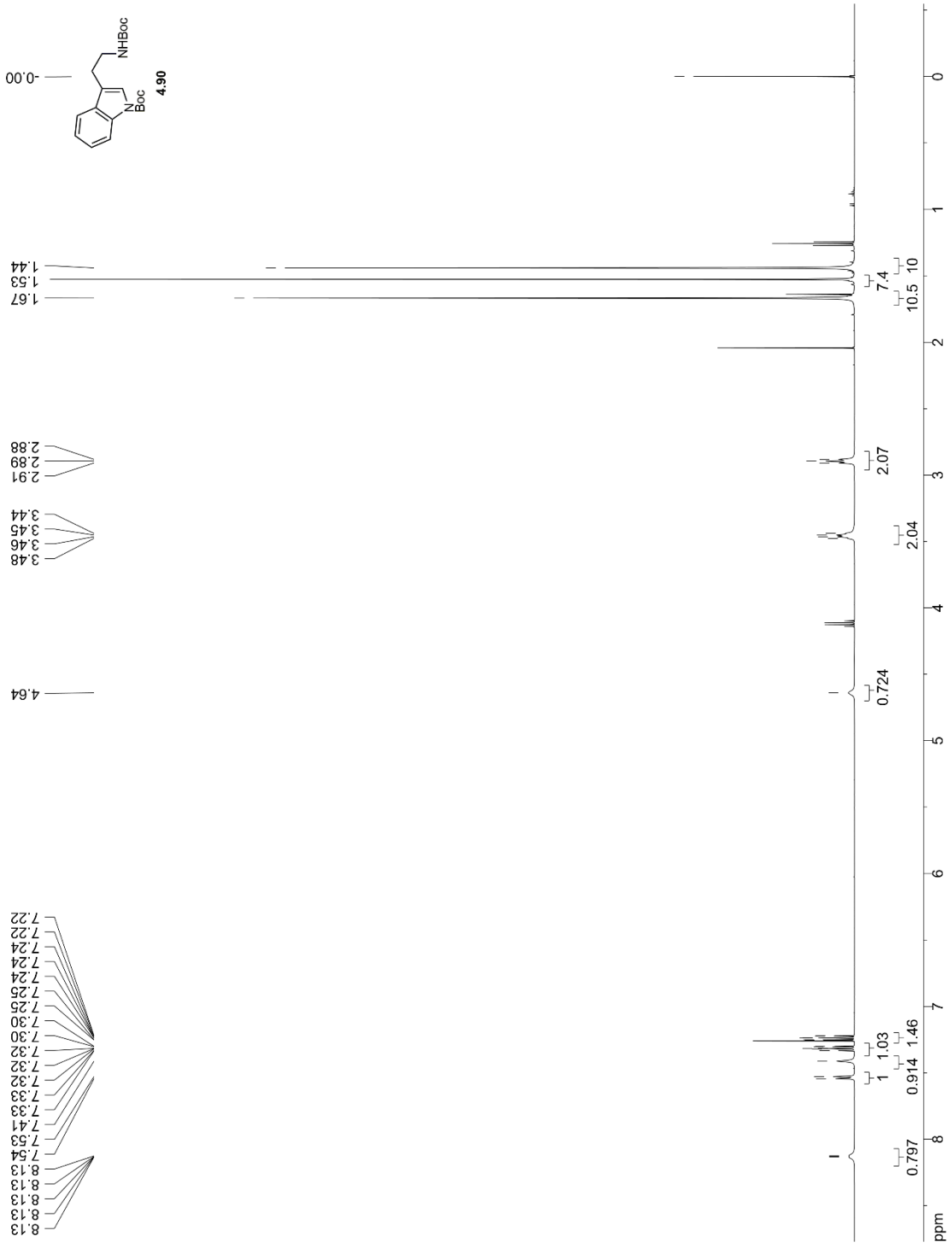
50
100
150
200
ppm


Br
Me
Me
H
Me
4.10
ppm


NHBoc
N
Boc
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-0.00
1.44
1.53
1.67
2.88
2.89
2.91
3.44
3.45
3.46
3.48
4.64
7.22
7.22
7.24
7.24
7.24
7.25
7.25
7.30
7.30
7.32
7.32
7.32
7.33
7.33
7.41
7.53
7.54
8.13
8.13
8.13
8.13
8.13
7.4
10.5
10
2.07
2.04
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0.914
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0.797
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2
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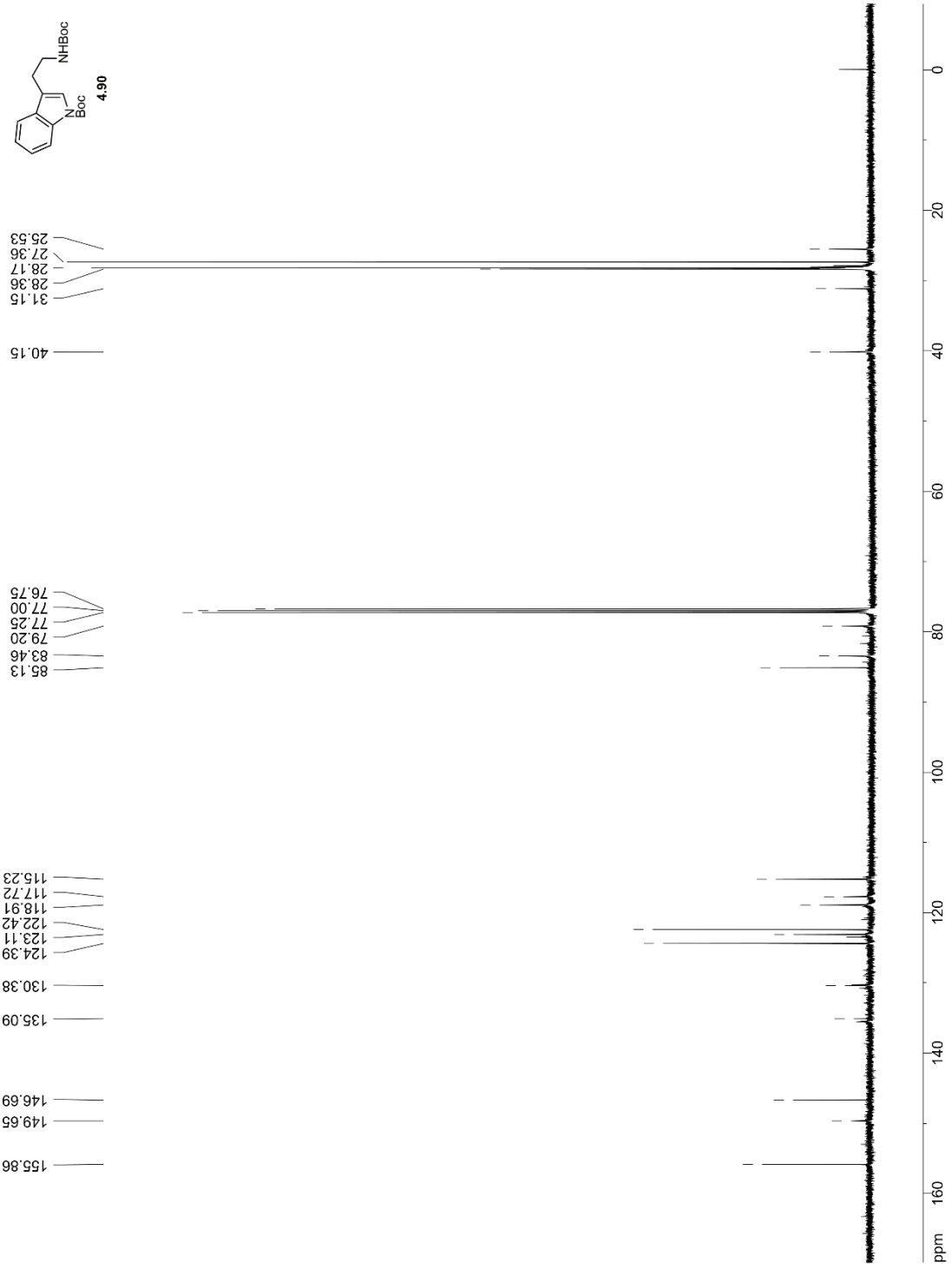
6
7
8
ppm


NHBoc
N
Boc
4.90
25.53
27.36
28.17
28.36
31.15
40.15
76.75
77.00
77.25
79.20
83.46
85.13
115.23
117.72
118.91
122.42
123.11
124.39
130.38
135.09
146.69
149.65
155.86
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40
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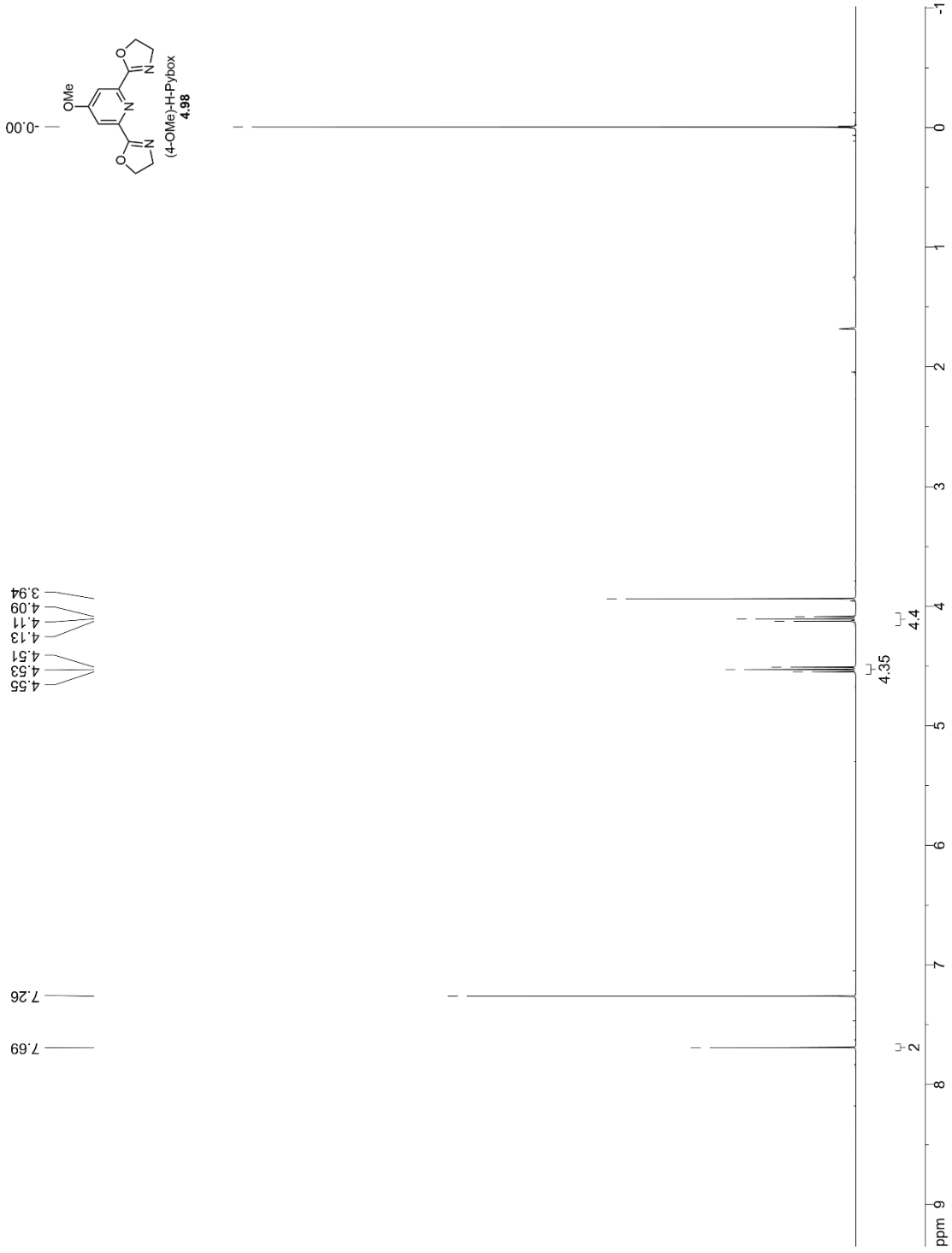
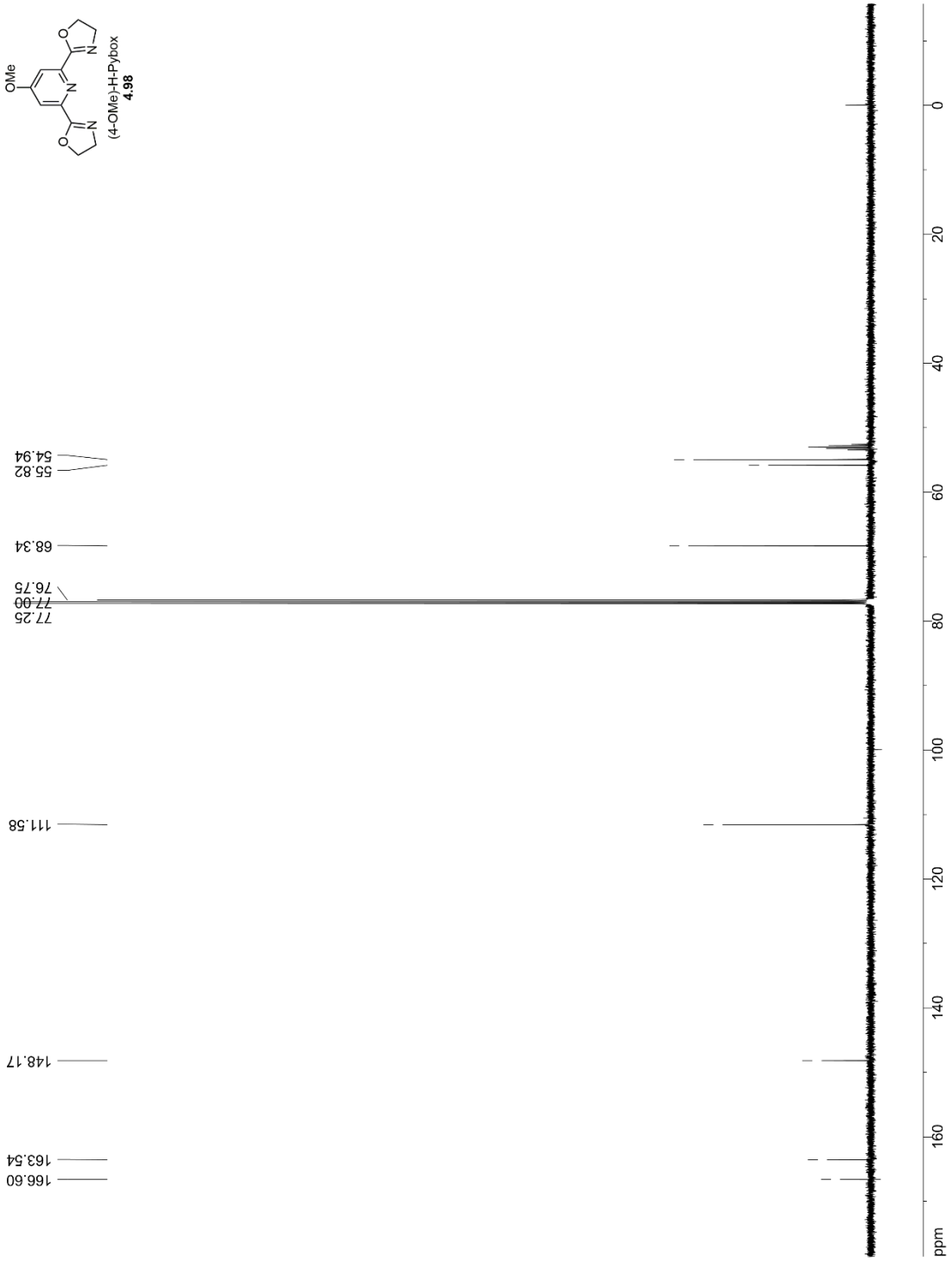
80
100
120
140
160
ppm


(4-OMe)-H-Pybox
4.98
OMe
-0.00
3.94
4.09
4.11
4.13
4.51
4.53
4.55
7.26
7.69
4.35
4.4
2
ppm


OMe
(4-OMe)-H-Pybox
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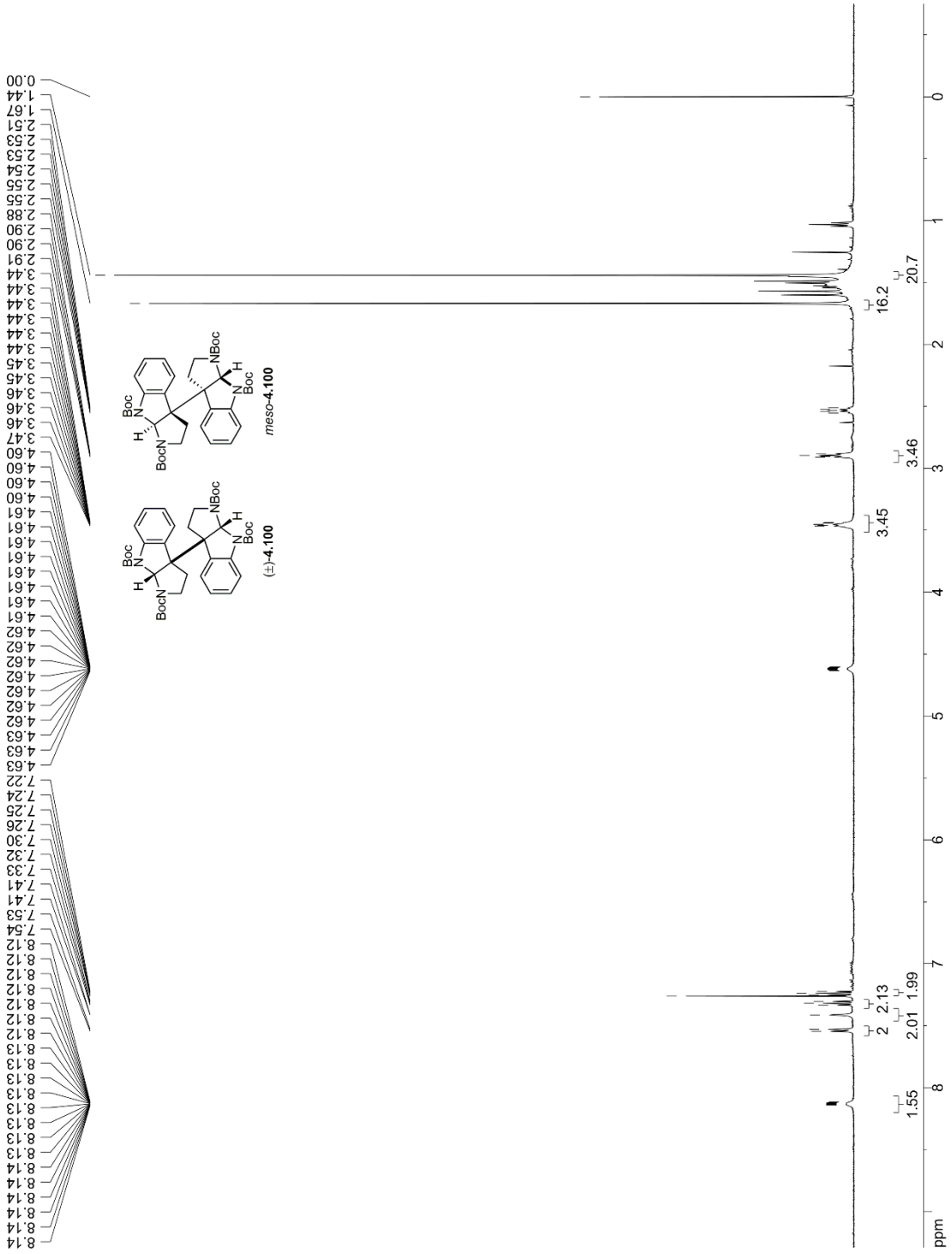
163.54
148.17
111.58
77.25
77.00
76.75
68.34
55.82
54.94
ppm


(±)-4.100
meso-4.100
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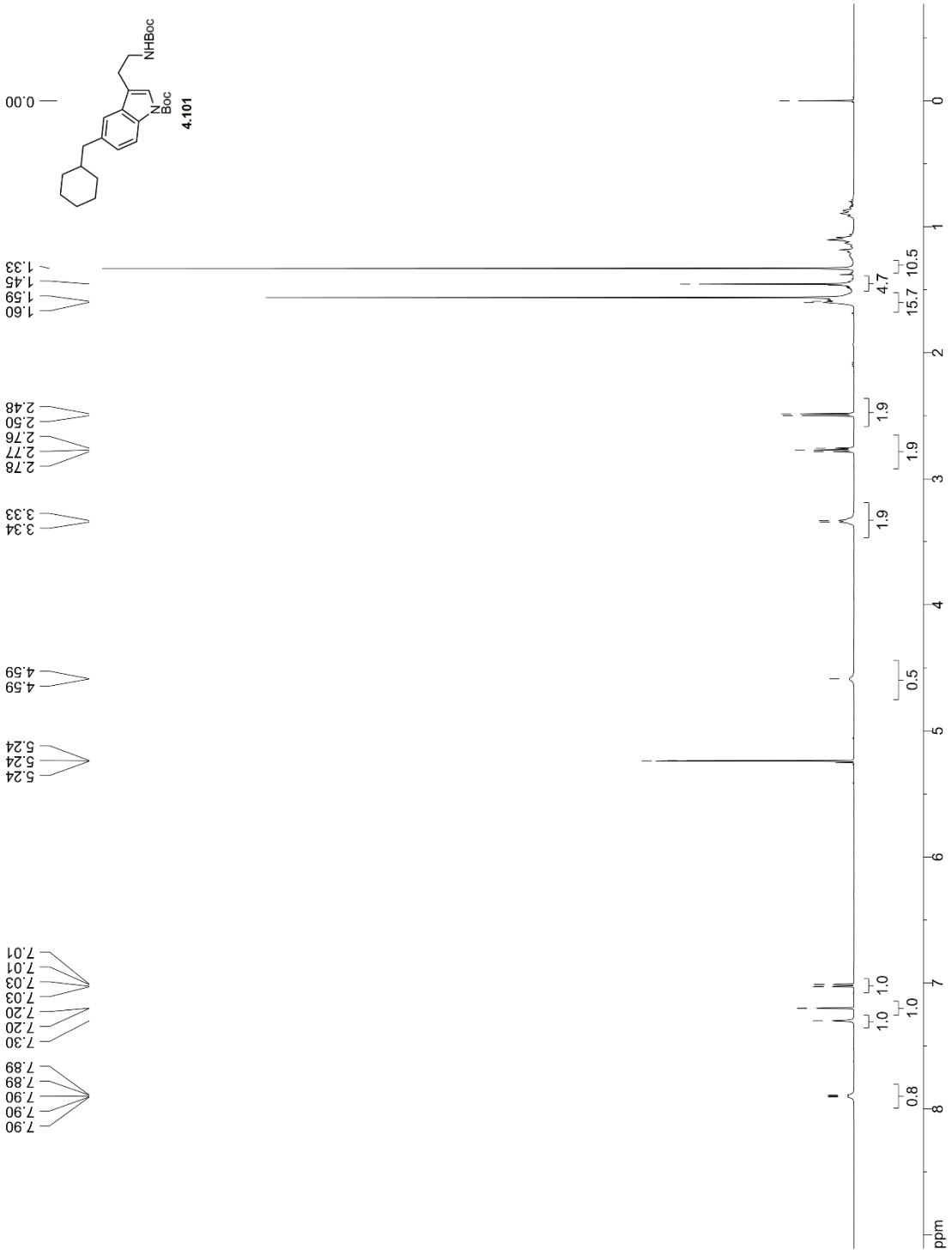
20.7
3.46
3.45
2
2.13
2.01
1.99
1.55
ppm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Boc
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1.60
2.48
2.50
2.76
2.77
2.78
3.33
3.34
4.59
5.24
5.24
7.01
7.01
7.03
7.03
7.20
7.20
7.30
7.89
7.90
7.90
7.90
4.7
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1.9
1.9
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1.0
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1.0
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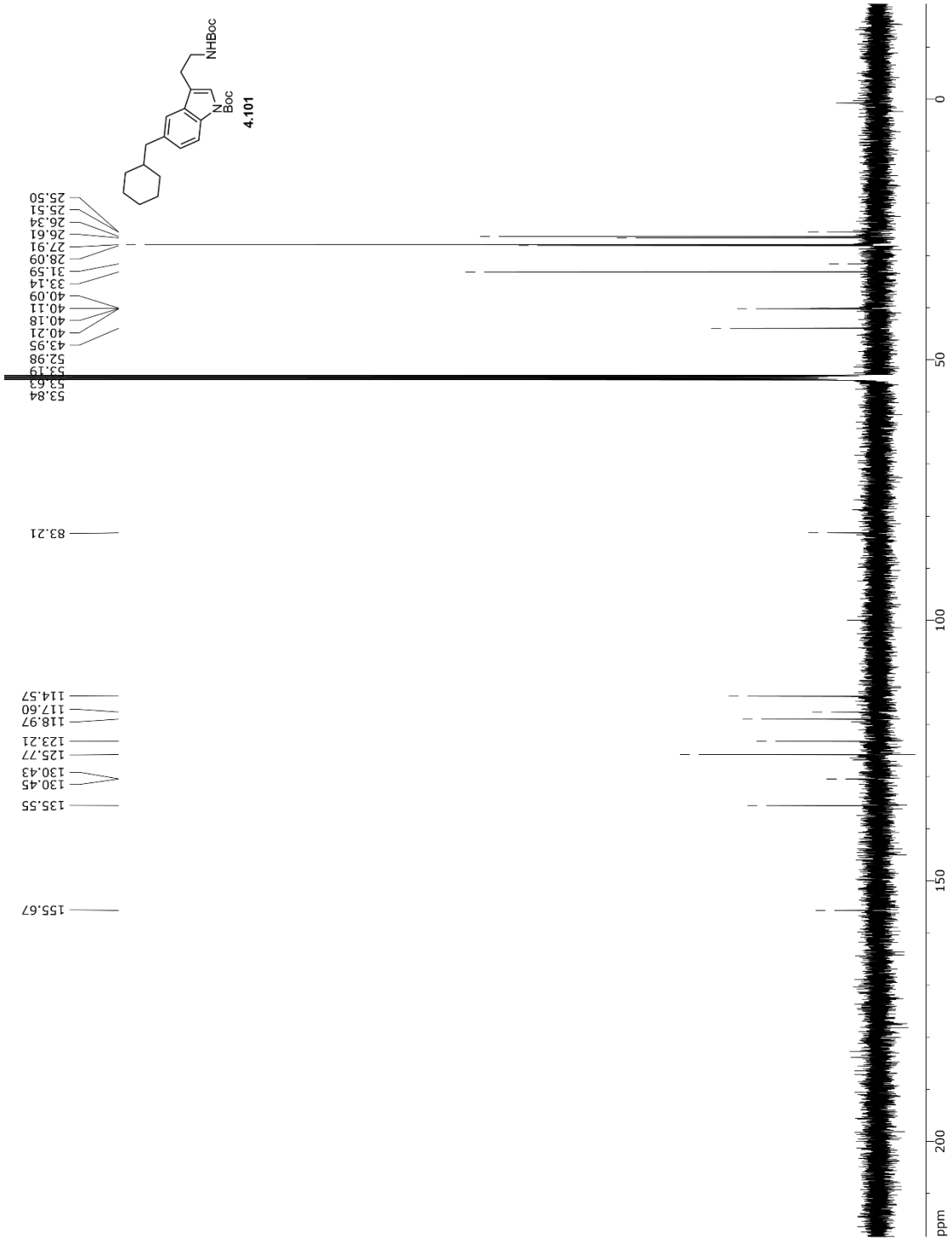
ppm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N
Boc
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27.91
28.09
31.59
33.14
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40.18
40.21
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53.19
53.63
53.84
83.21
114.57
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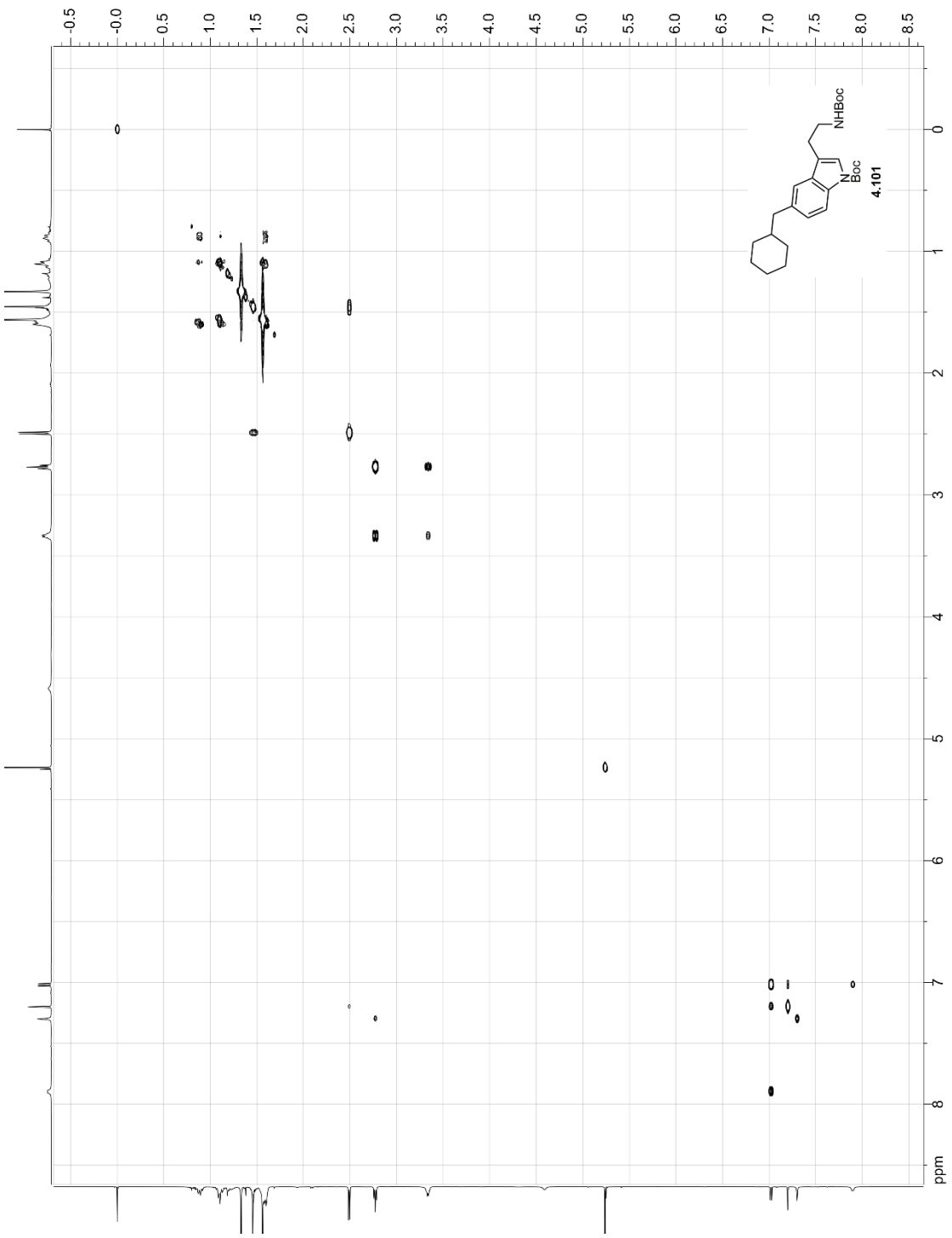
123.21
125.77
130.43
130.45
135.55
155.67
0
50
100
150
200
ppm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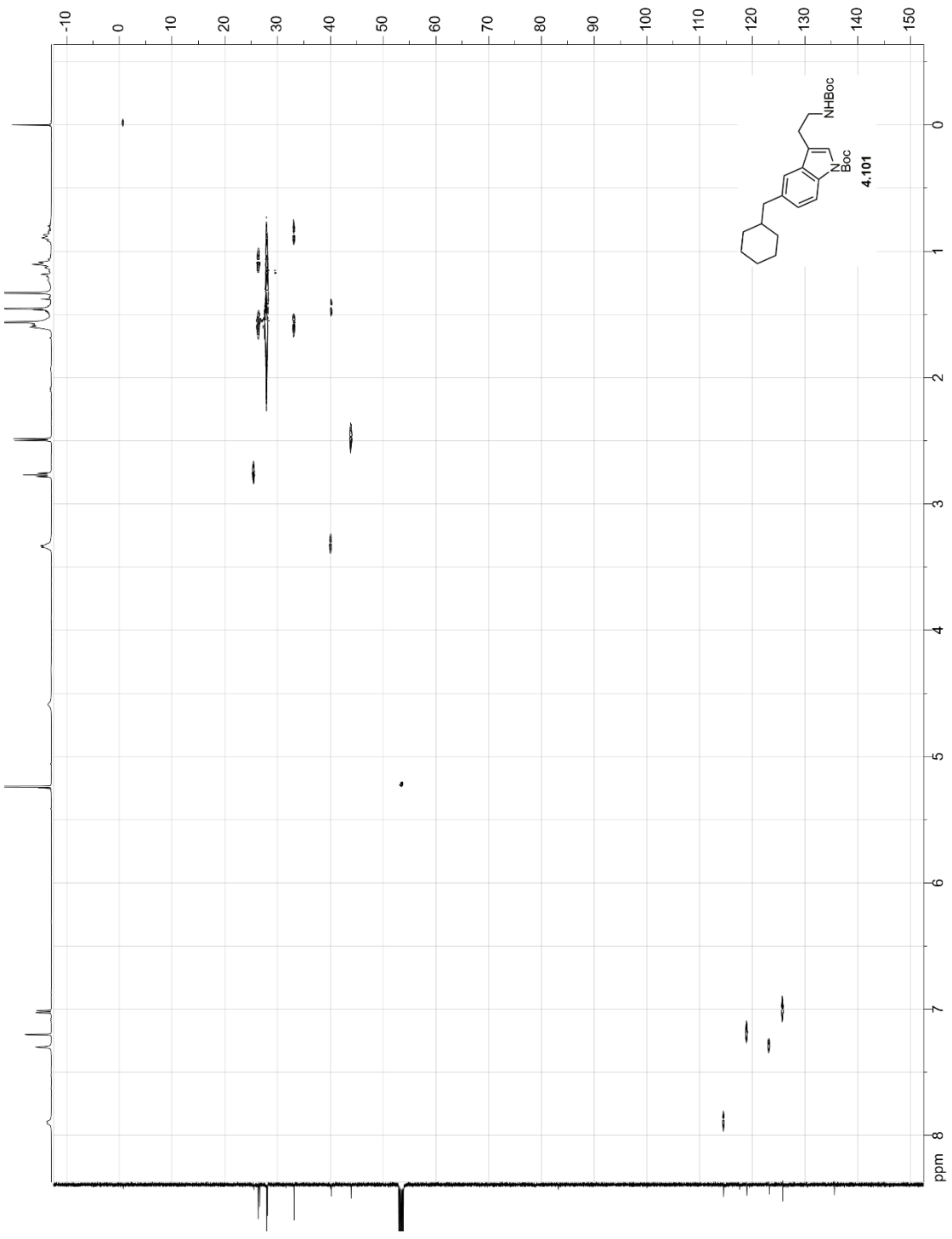
Boc
4.101
ppm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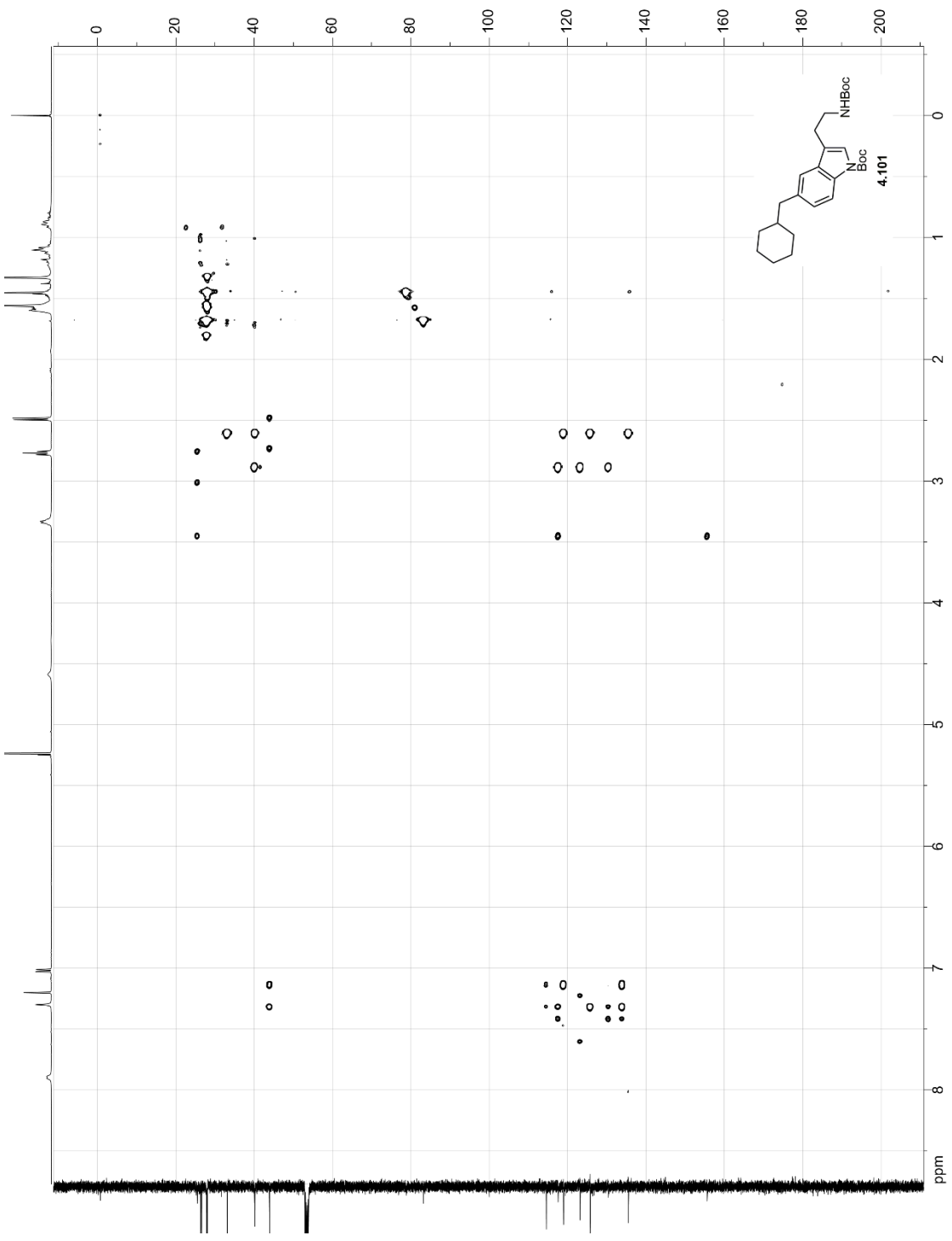
N
Boc
4.101
ppm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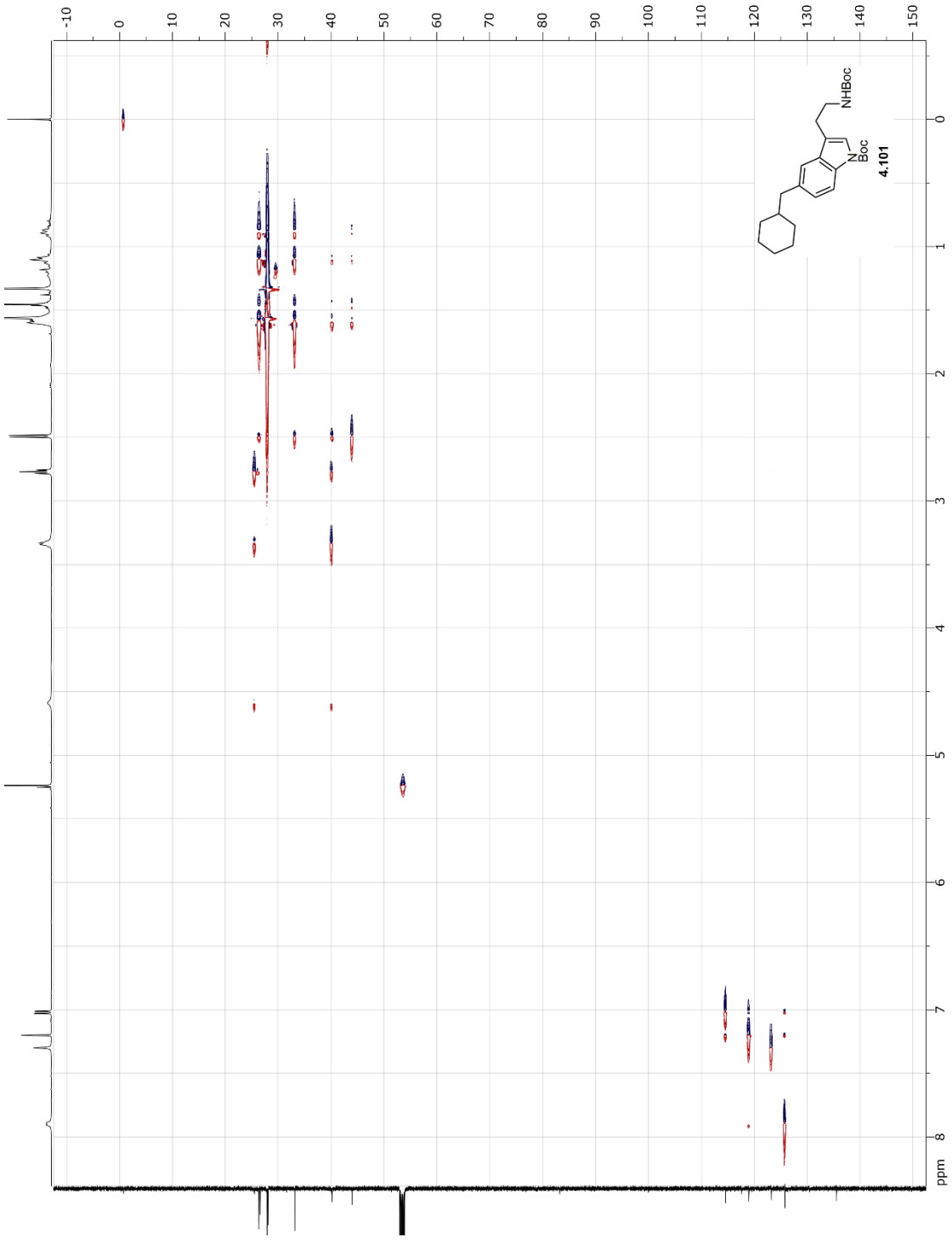
Boc
4.101
ppm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Boc
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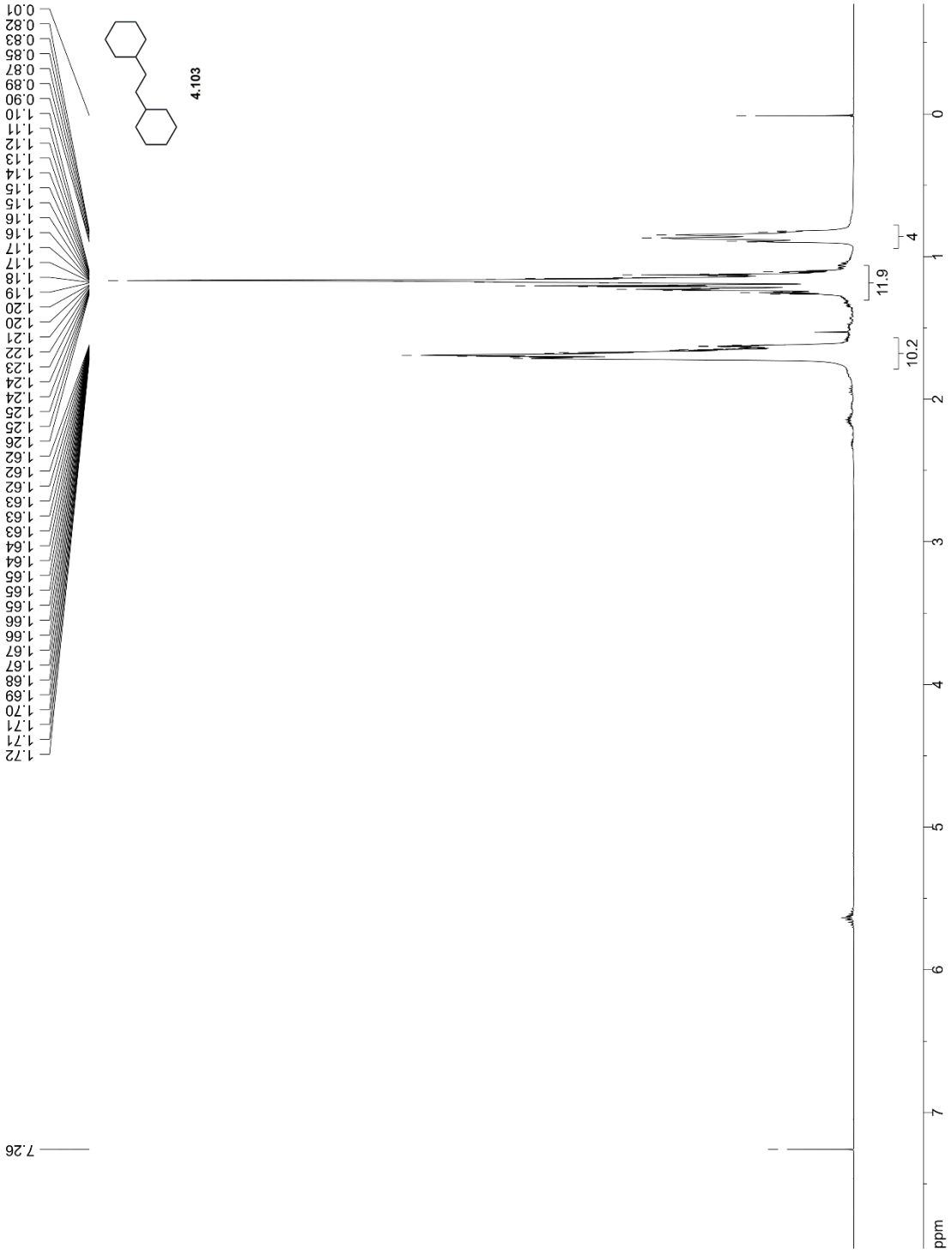
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11.9
10.2
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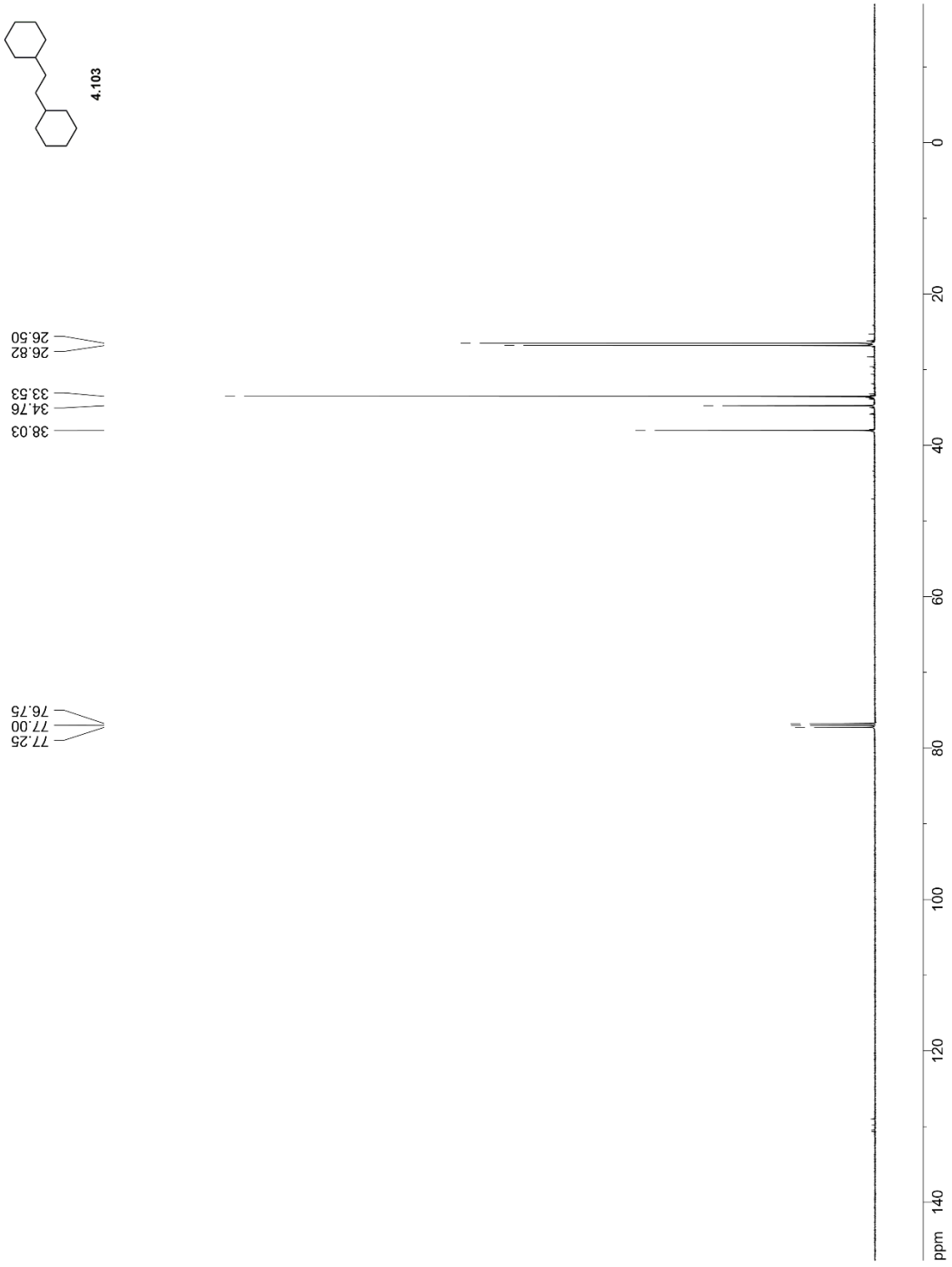
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26.50
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76.75
77.00
77.25
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20
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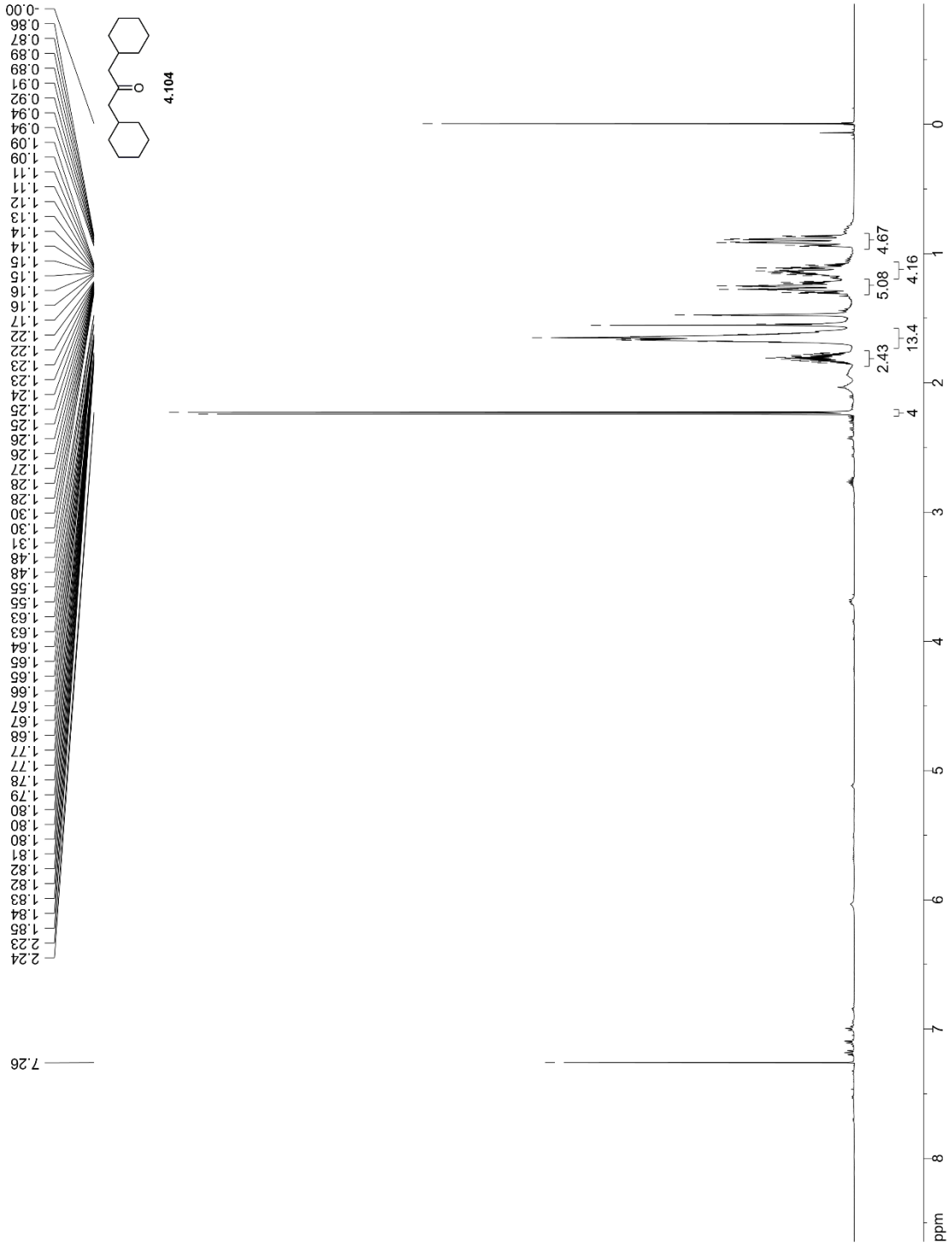
120
140
ppm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4.67
4.16
5.08
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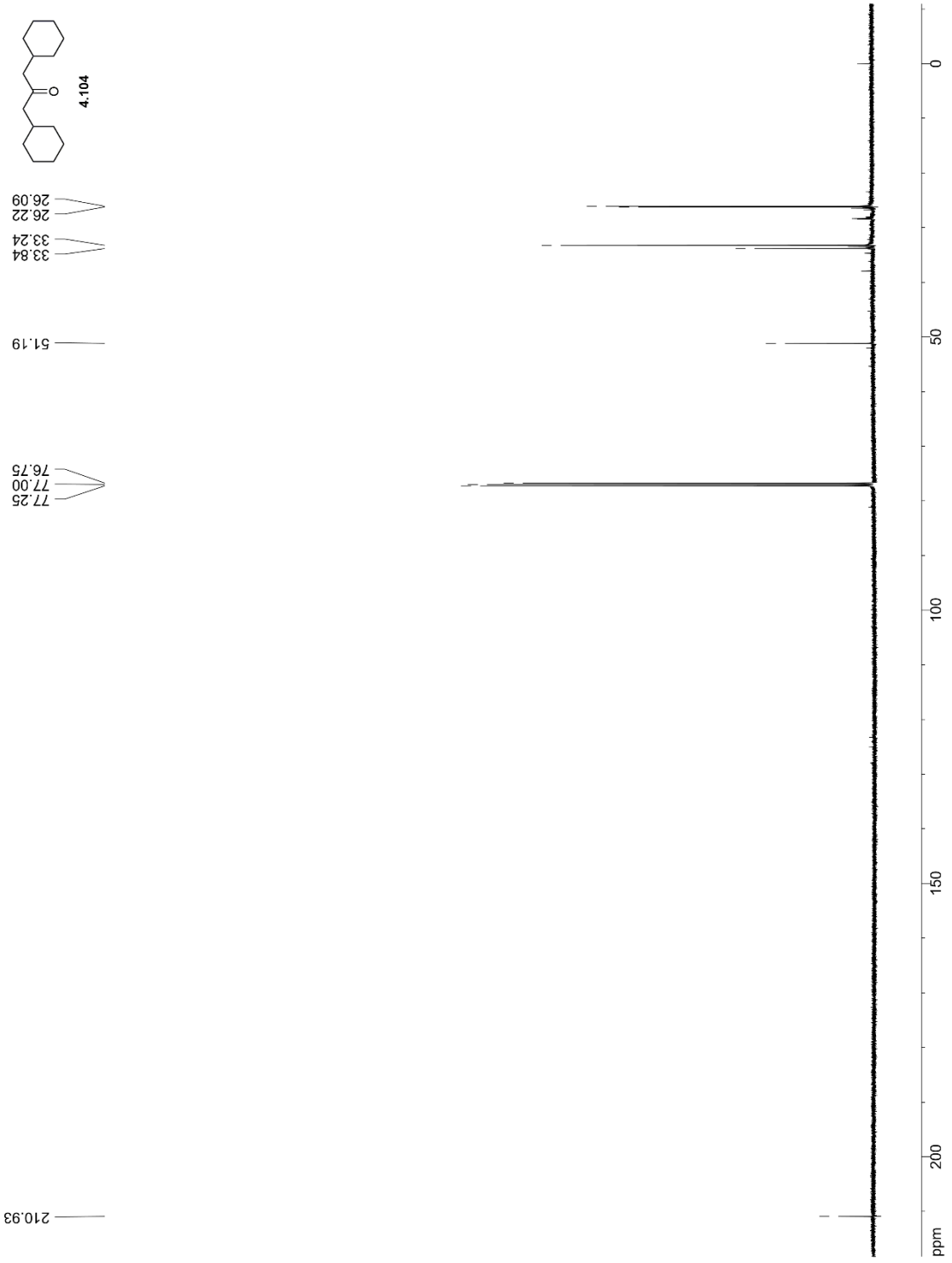
2.43
4
ppm


4.104
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200
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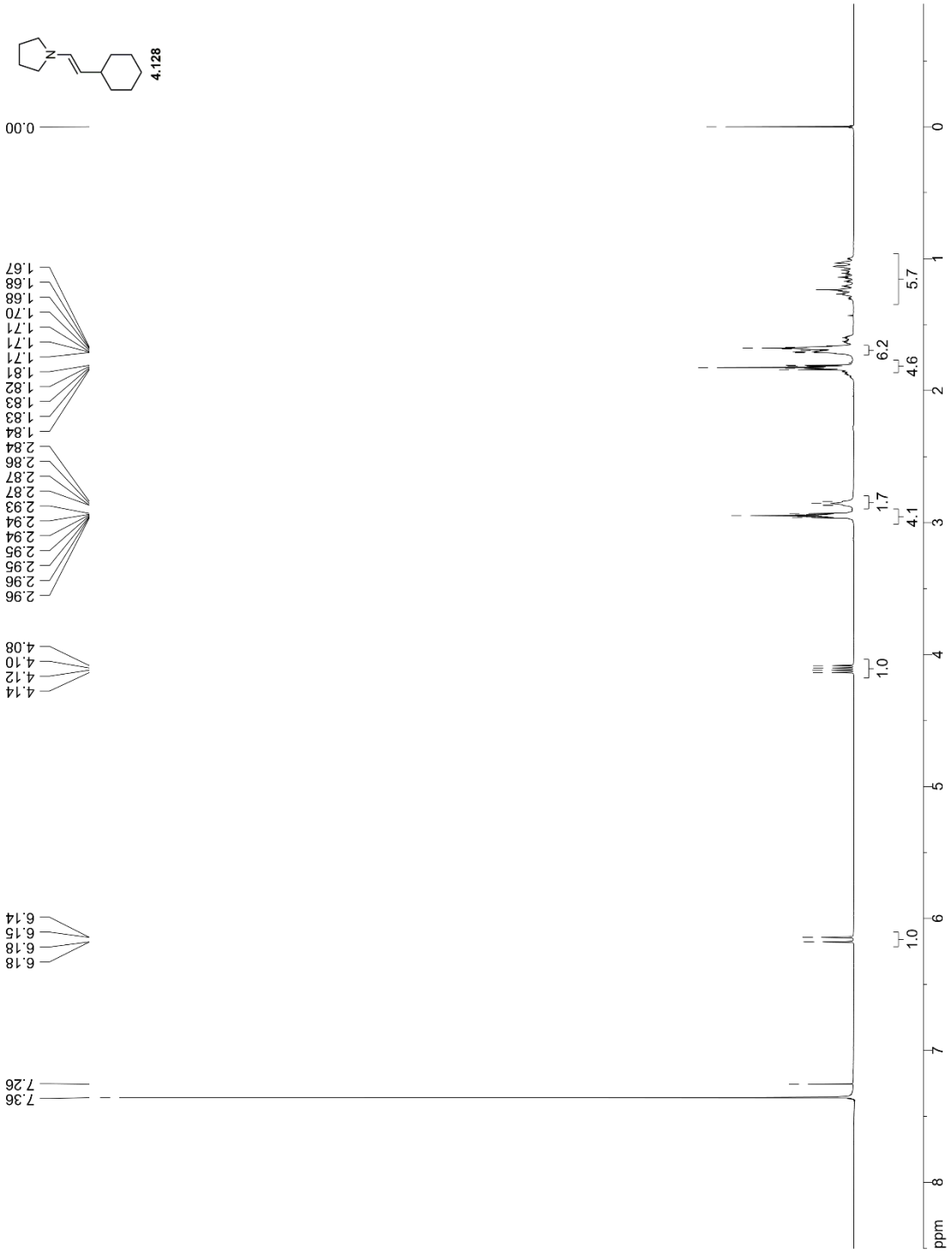
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1.71
1.71
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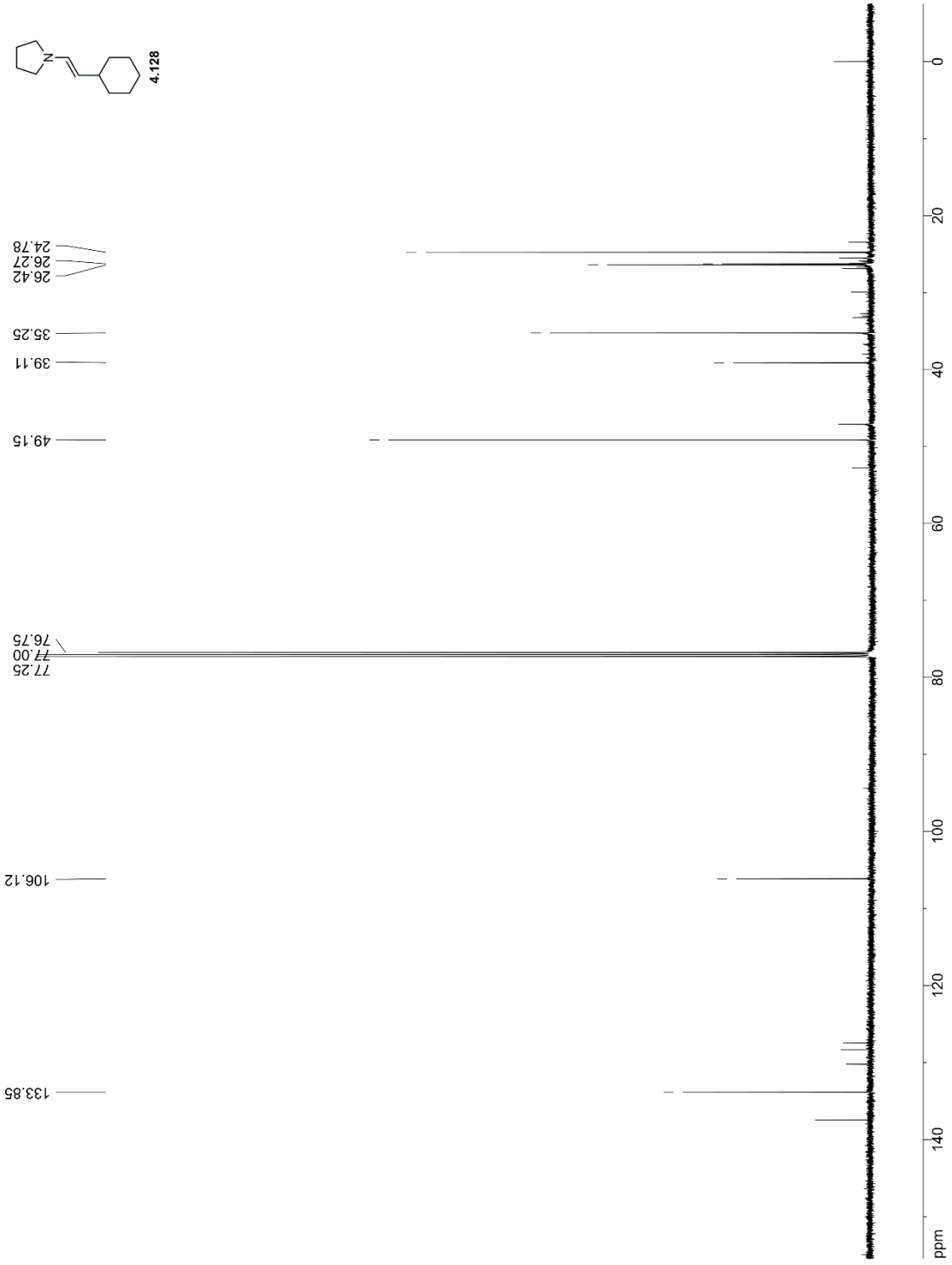
1.81
1.82
1.83
1.83
1.84
2.84
2.86
2.87
2.87
2.93
2.94
2.94
2.95
2.95
2.96
2.96
4.08
4.10
4.12
4.14
6.14
6.15
6.18
6.18
7.26
7.36
5.7
6.2
4.6
1.7
4.1
1.0
1.0
ppm


4.128
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26.42
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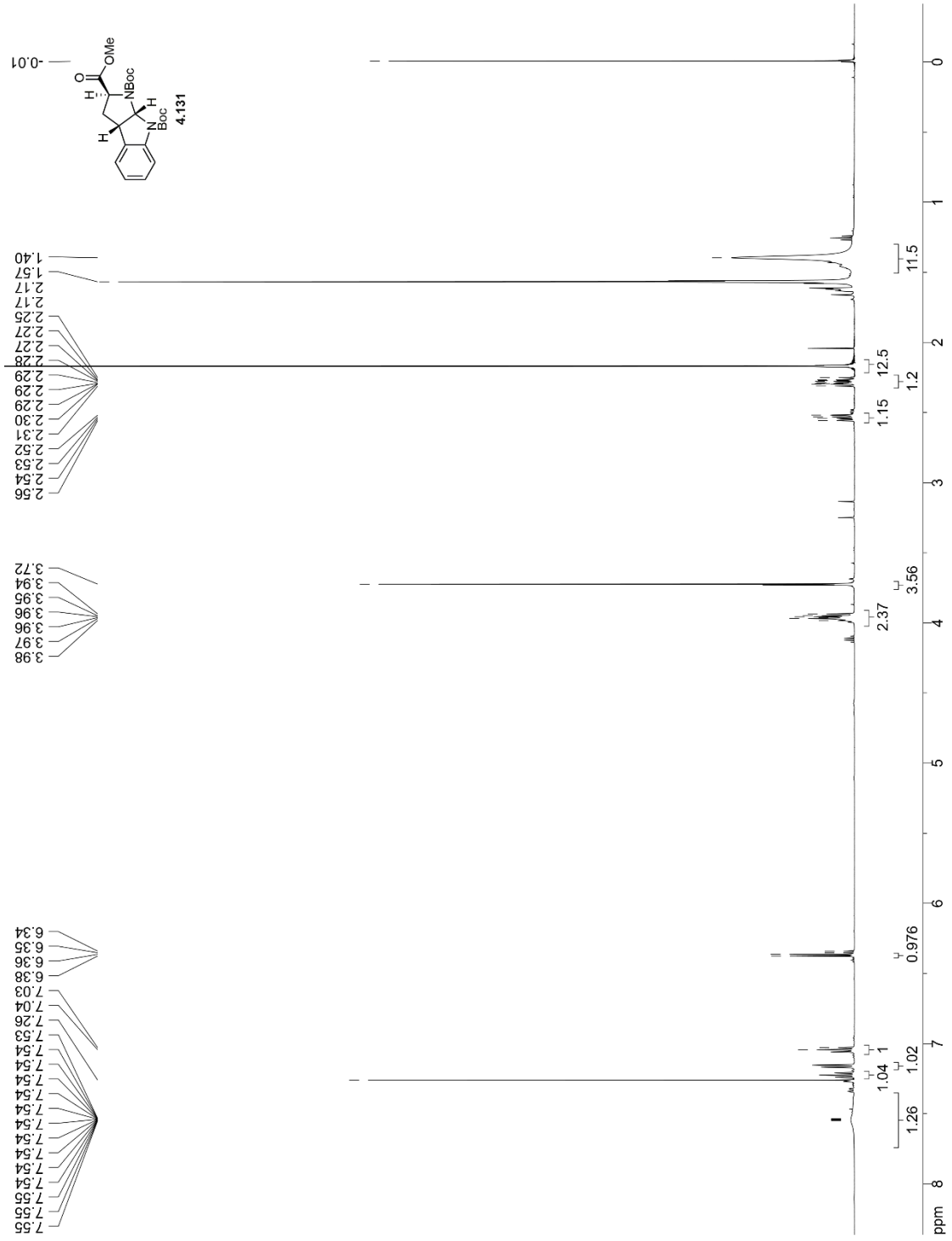
39.11
49.15
76.75
77.00
77.25
106.12
133.85
0
20
40
60
80
100
120
140
ppm


4.131
-0.01
1.40
1.57
2.17
2.17
2.25
2.27
2.27
2.28
2.29
2.29
2.29
2.30
2.31
2.52
2.53
2.54
2.56
3.72
3.94
3.95
3.96
3.96
3.97
3.98
6.34
6.35
6.36
6.38
7.03
7.04
7.26
7.53
7.54
7.54
7.54
7.54
7.54
7.54
7.54
7.54
7.54
7.55
7.55
11.5
12.5
1.2
1.15
3.56
2.37
0.976
1
1.04
1.02
1.26
0
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2
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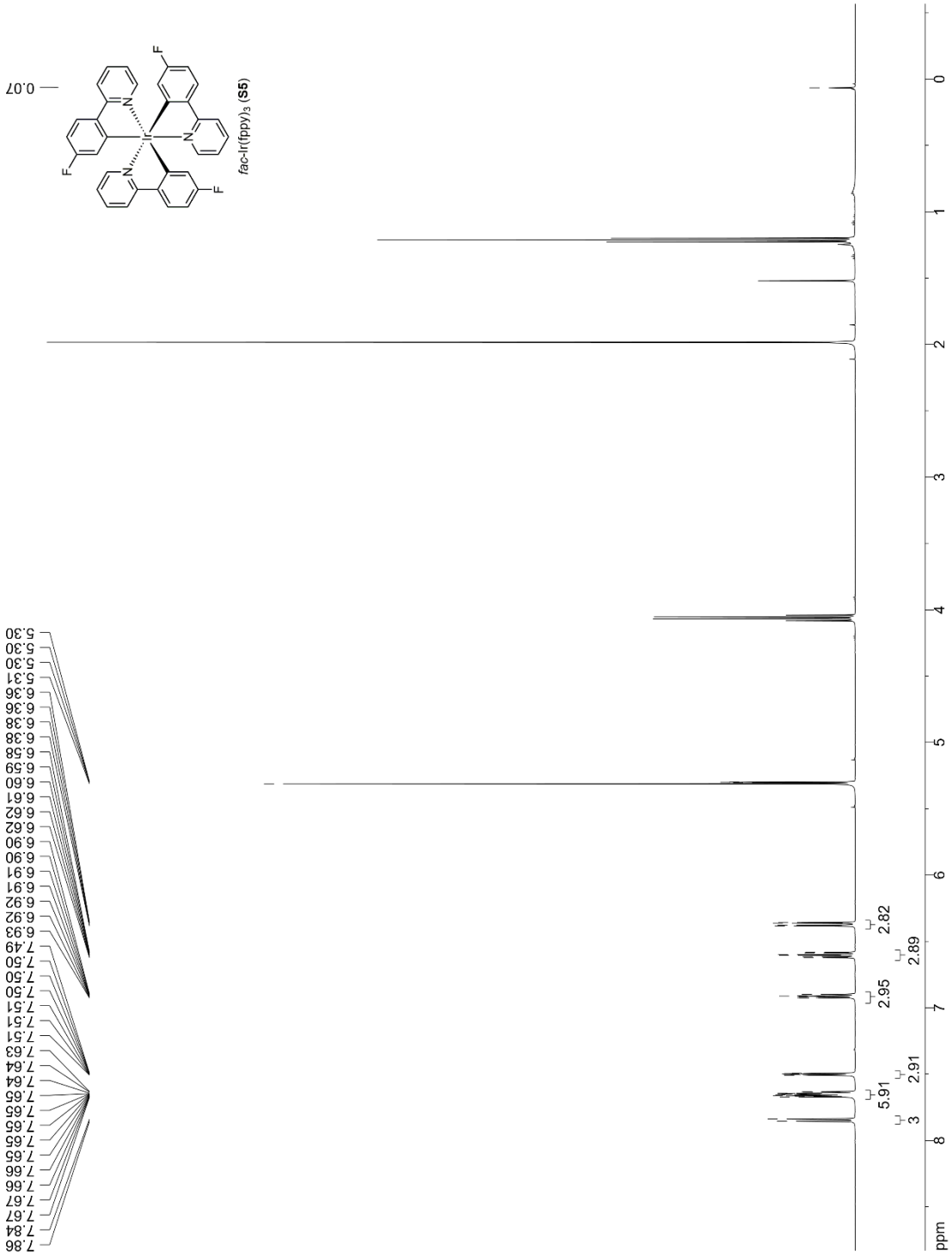
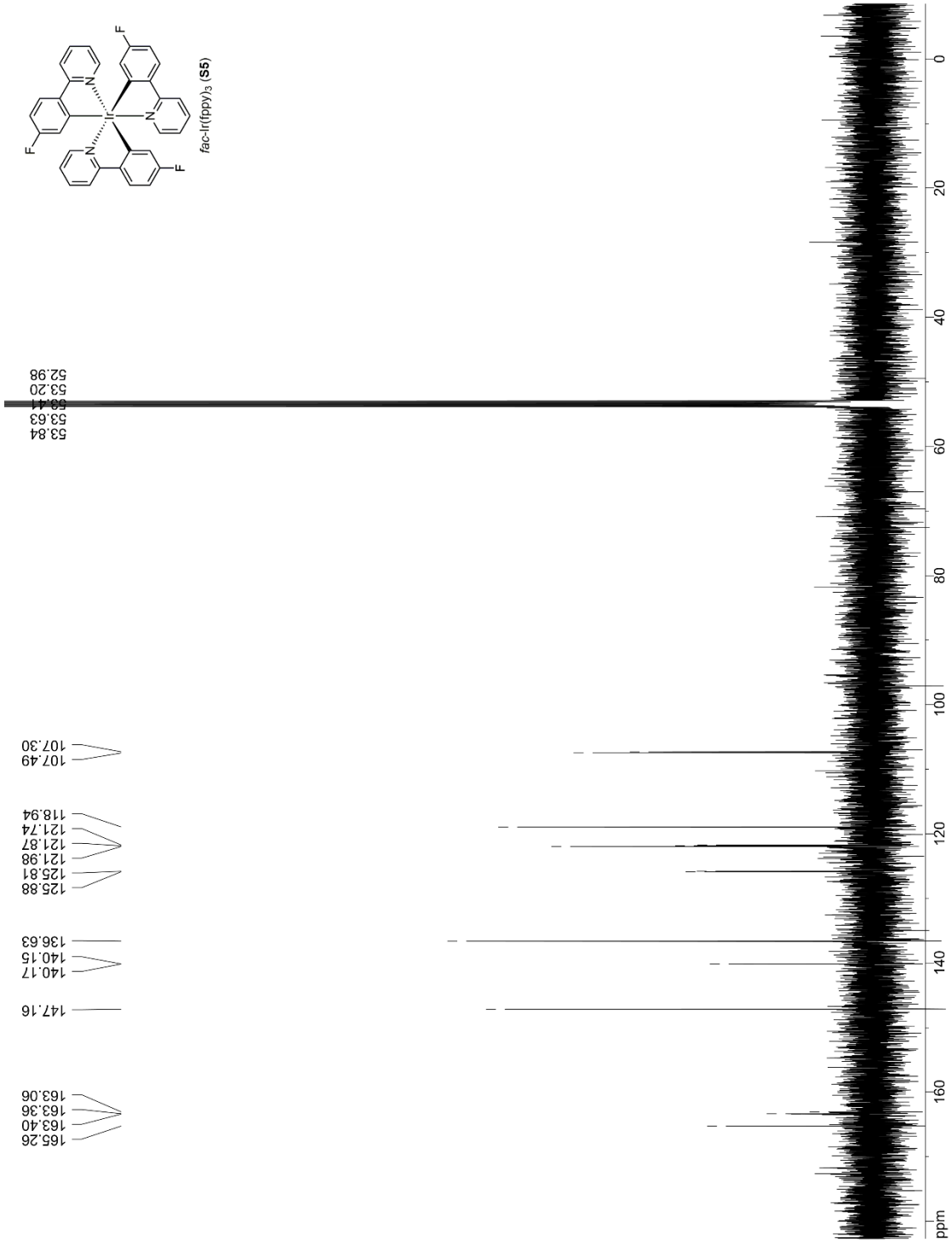
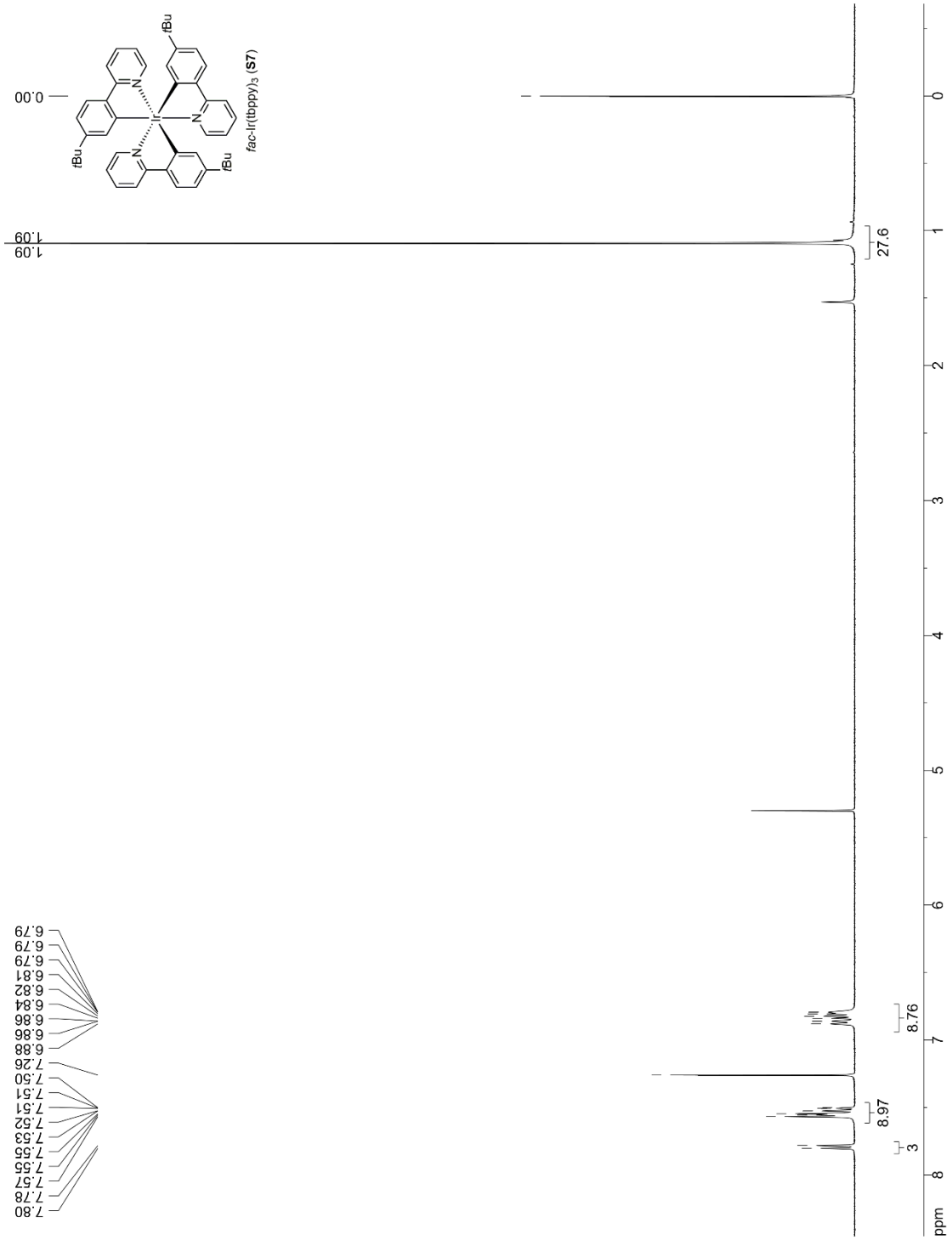
4
5
6
7
8
ppm


0.07
fac-Ir(fppy)3 (S5)
F
N
Ir
7.86
7.84
7.67
7.67
7.67
7.66
7.66
7.66
7.65
7.65
7.65
7.65
7.65
7.64
7.64
7.63
7.51
7.51
7.50
7.50
7.50
7.49
6.93
6.92
6.92
6.91
6.91
6.90
6.90
6.62
6.62
6.61
6.60
6.59
6.58
6.38
6.38
6.36
6.36
5.31
5.30
5.30
5.30
5.30
2.82
2.89
2.95
2.91
5.91
3
ppm


fac-Ir(fppy)3 (S5)
F
N
Ir
ppm
0
20
40
60
80
100
120
140
160
53.84
53.63
53.41
53.20
52.98
107.49
107.30
118.94
121.74
121.87
121.98
125.81
125.88
136.63
140.15
140.17
147.16
163.06
163.36
163.40
165.26


fac-Ir(tbppy)3 (S7)
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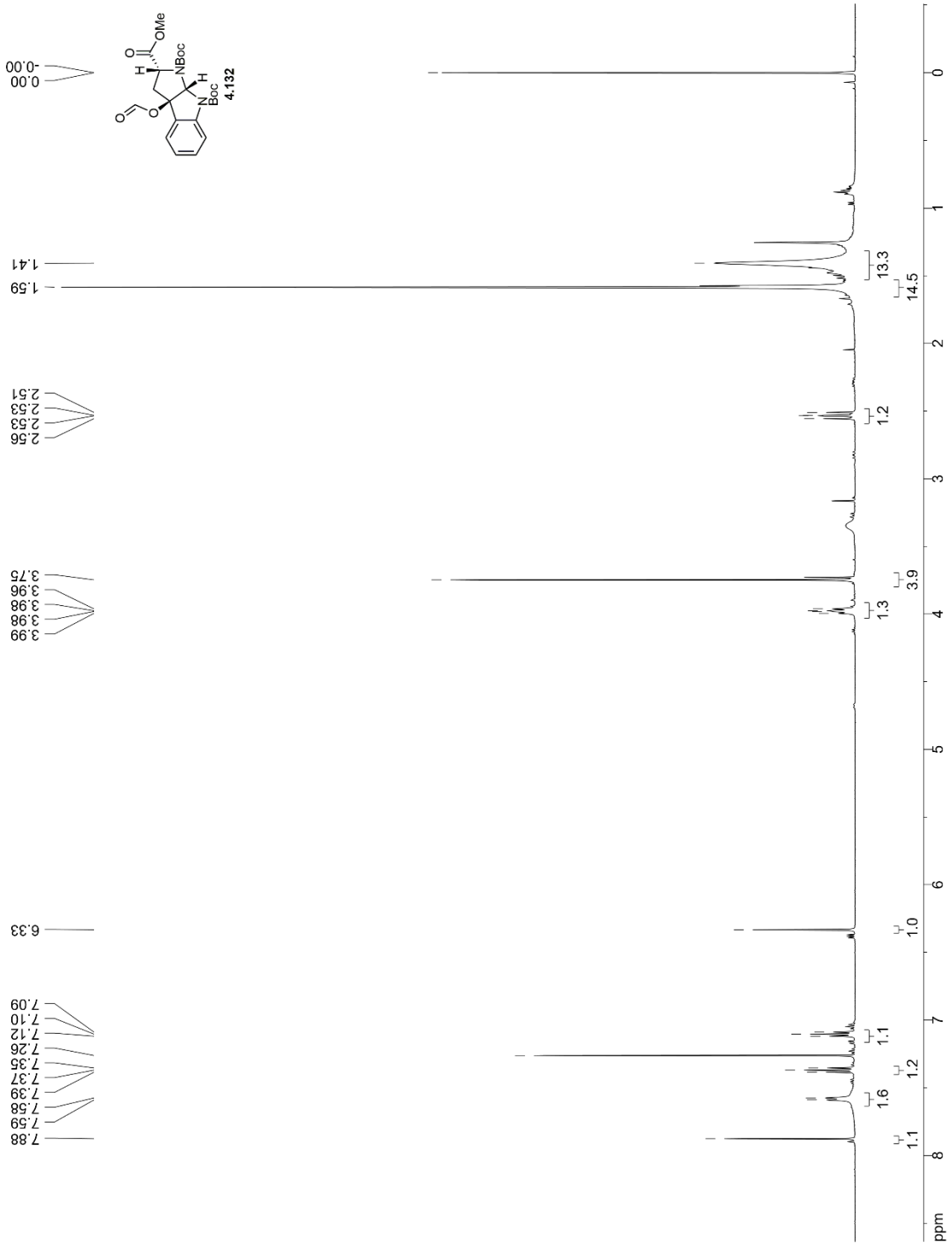
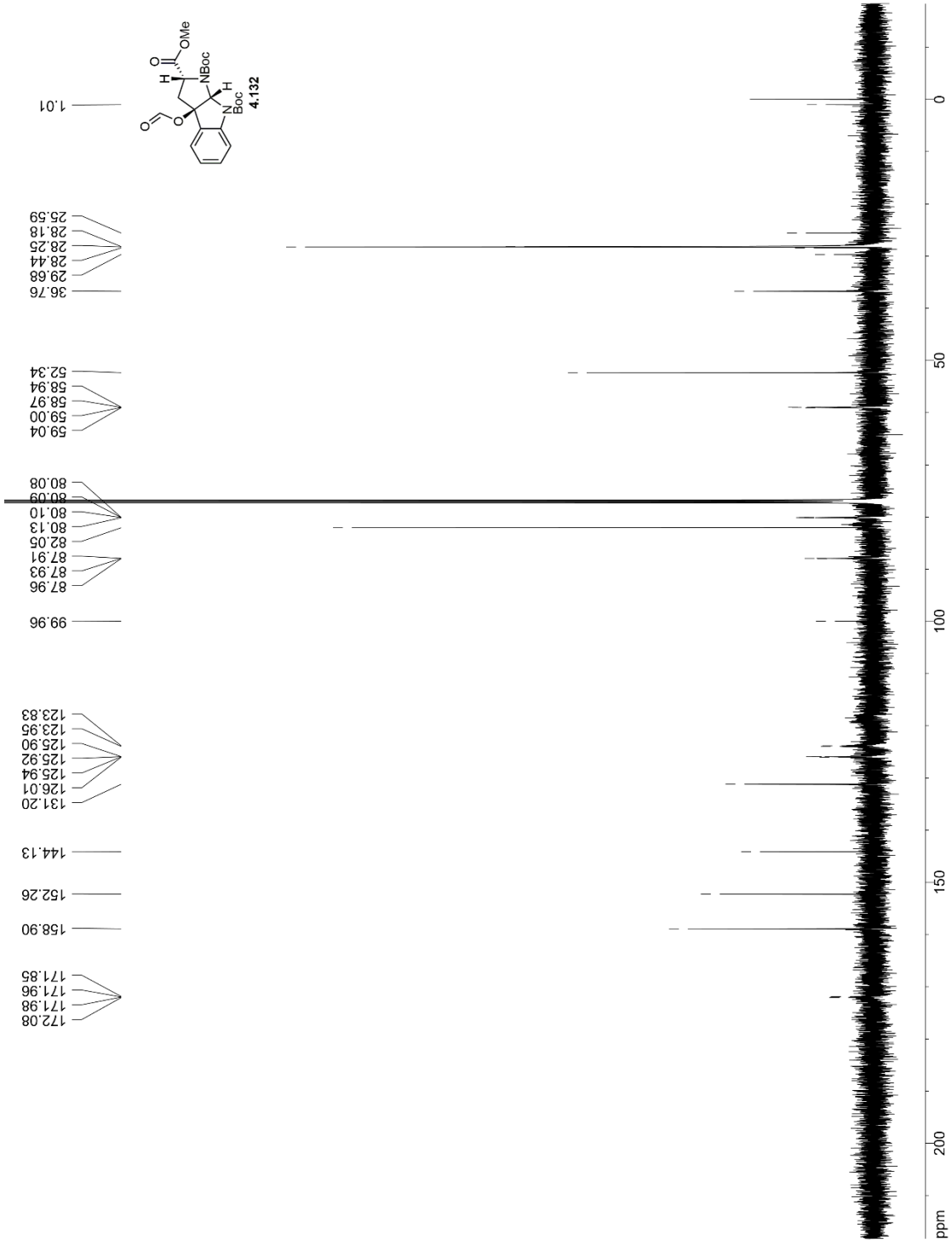
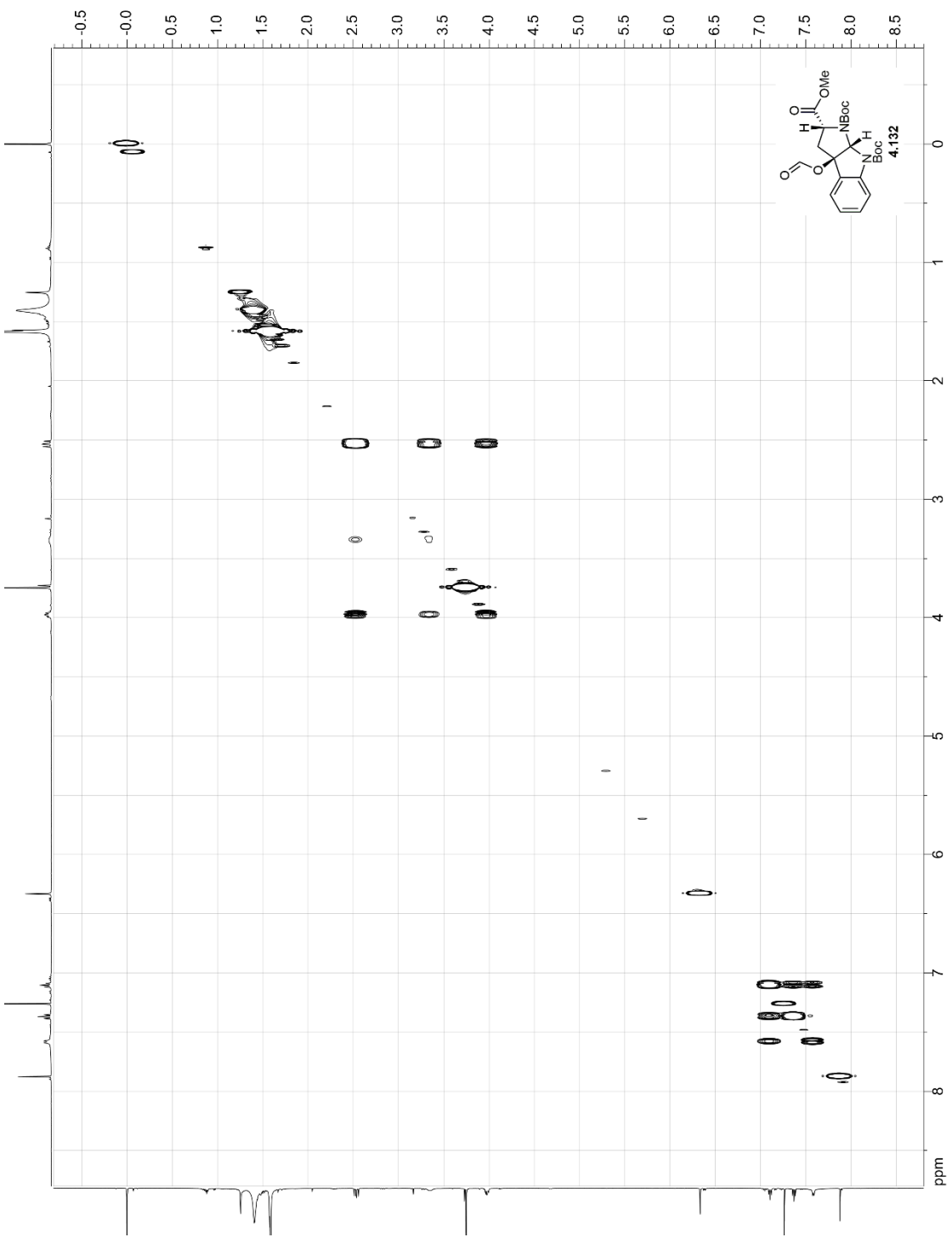
1.09
1.09
27.6
8.76
8.97
3
6.79
6.79
6.79
6.81
6.82
6.84
6.86
6.86
6.88
7.26
7.50
7.51
7.51
7.52
7.53
7.55
7.55
7.57
7.78
7.80
ppm


4.132
0.00
-0.00
1.41
1.59
2.51
2.53
2.53
2.56
3.75
3.96
3.98
3.98
3.99
6.33
7.09
7.10
7.12
7.26
7.35
7.37
7.39
7.58
7.59
7.88
13.3
14.5
1.2
3.9
1.3
1.0
1.1
1.2
1.6
1.1
ppm


4.132
1.01
25.59
28.18
28.25
28.44
29.68
36.76
52.34
58.94
58.97
59.00
59.04
80.08
80.09
80.10
80.13
82.05
87.91
87.93
87.96
99.96
123.83
123.95
125.90
125.92
125.94
126.01
131.20
144.13
152.26
158.90
171.85
171.96
171.98
172.08
0
50
100
150
200
ppm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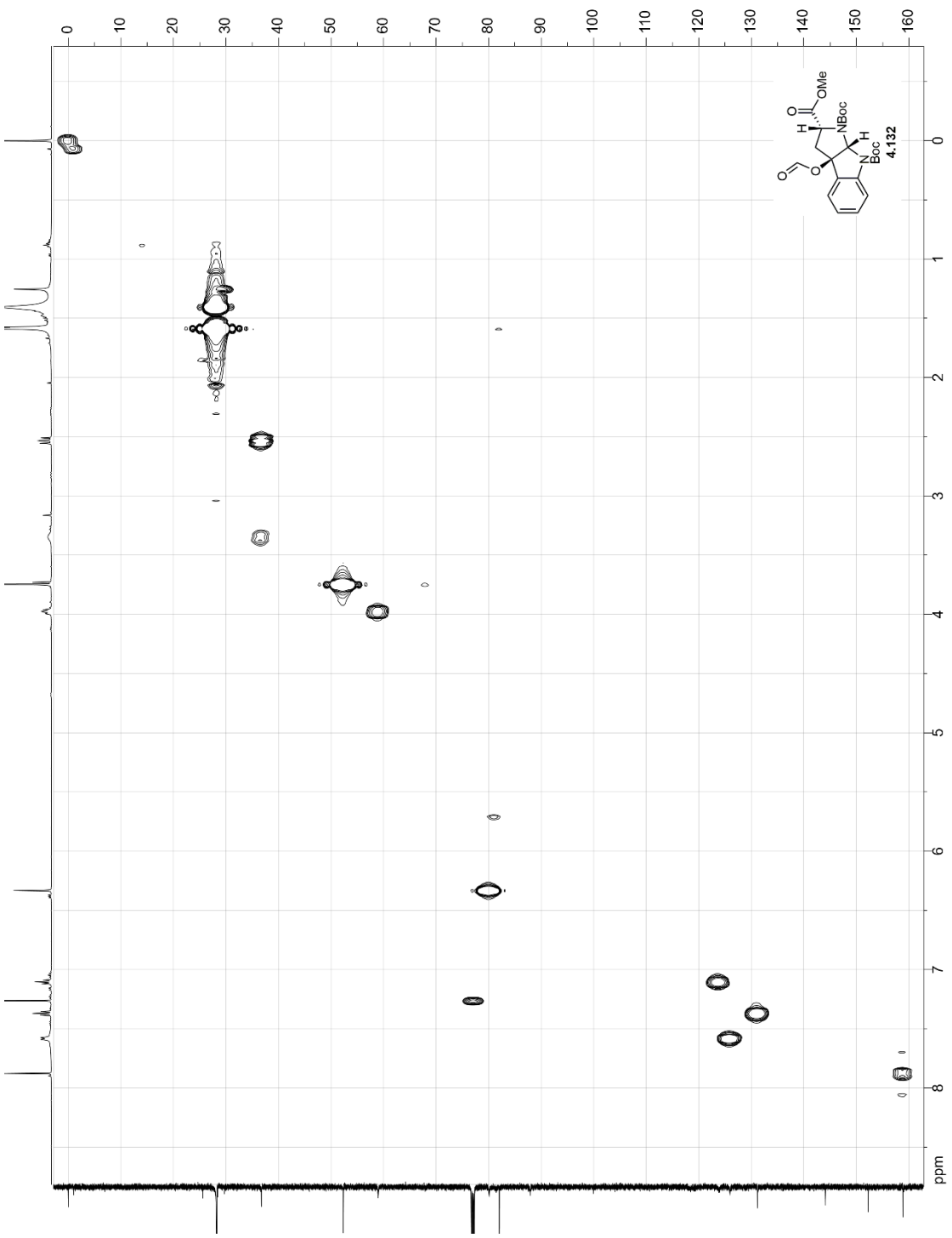
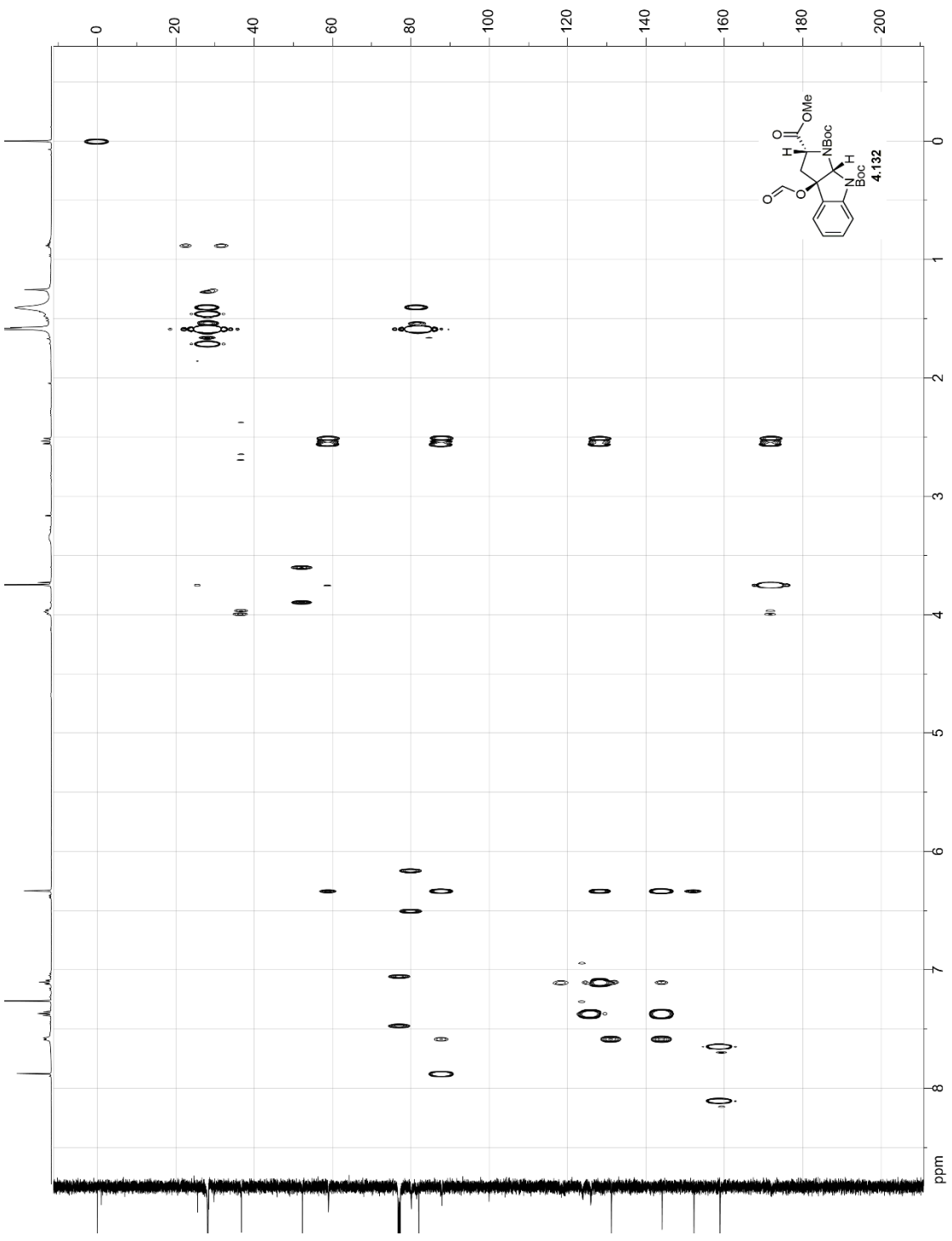
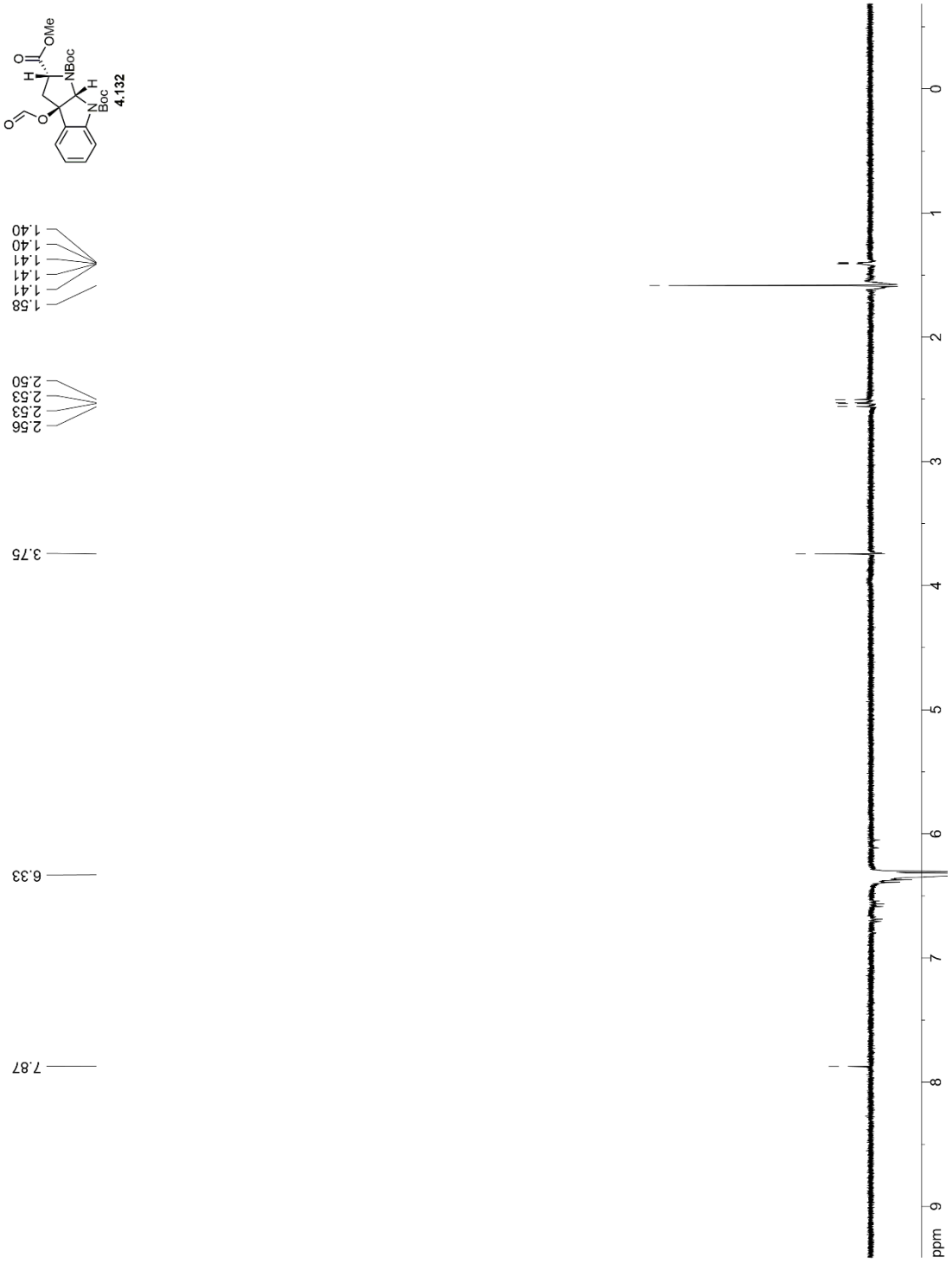
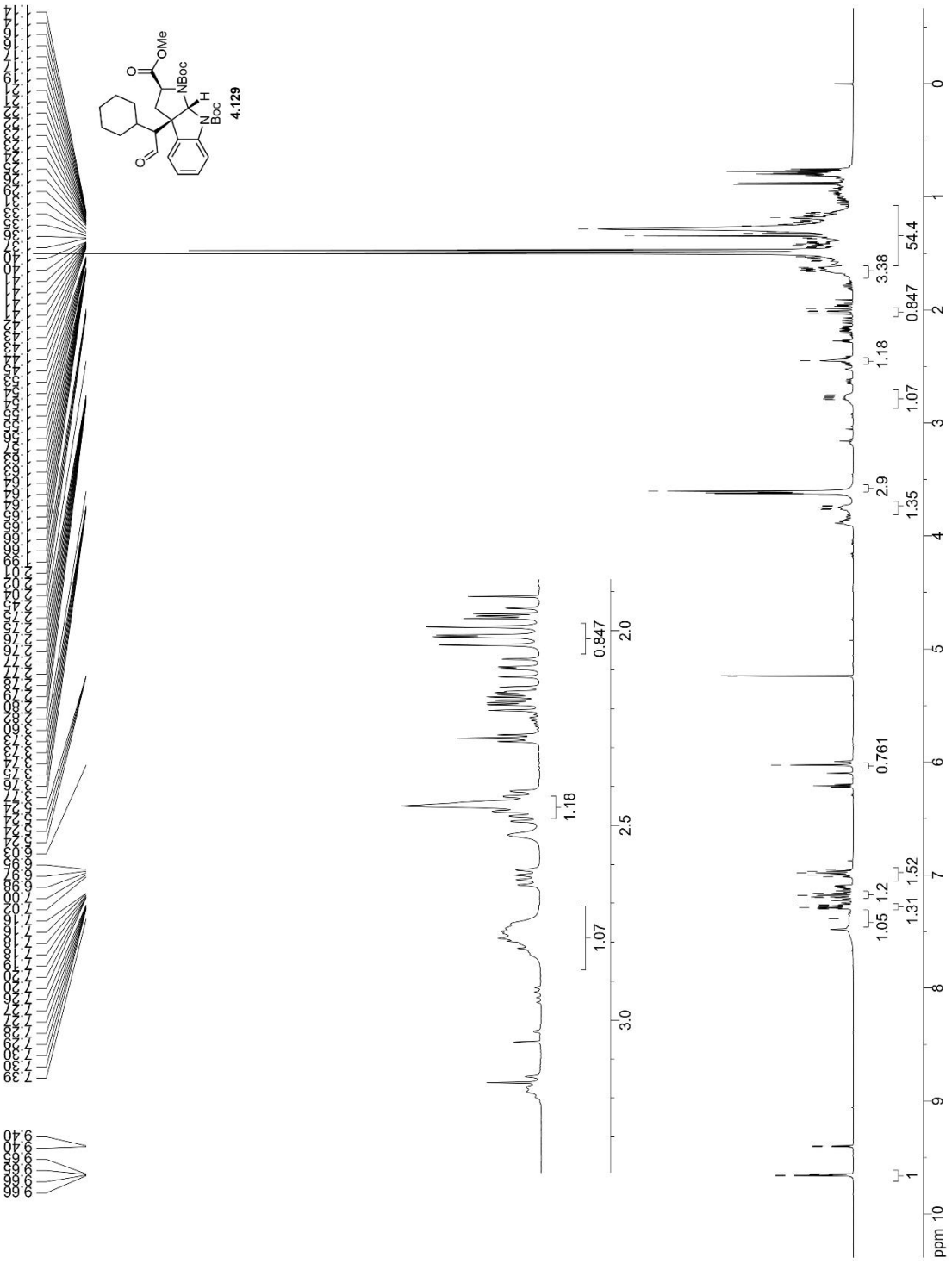
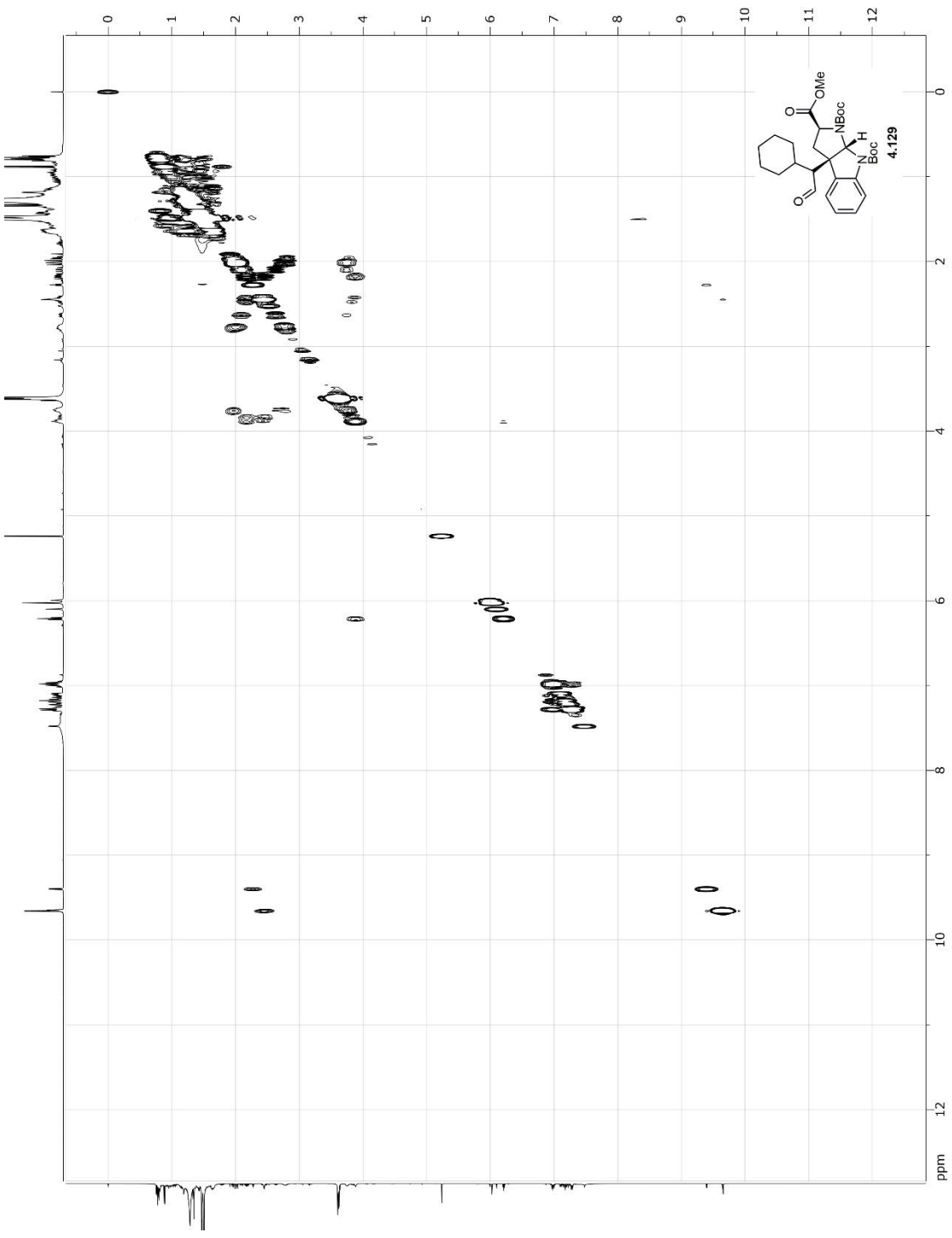
-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
ppm
OMe
NBoc
Boc
4.132

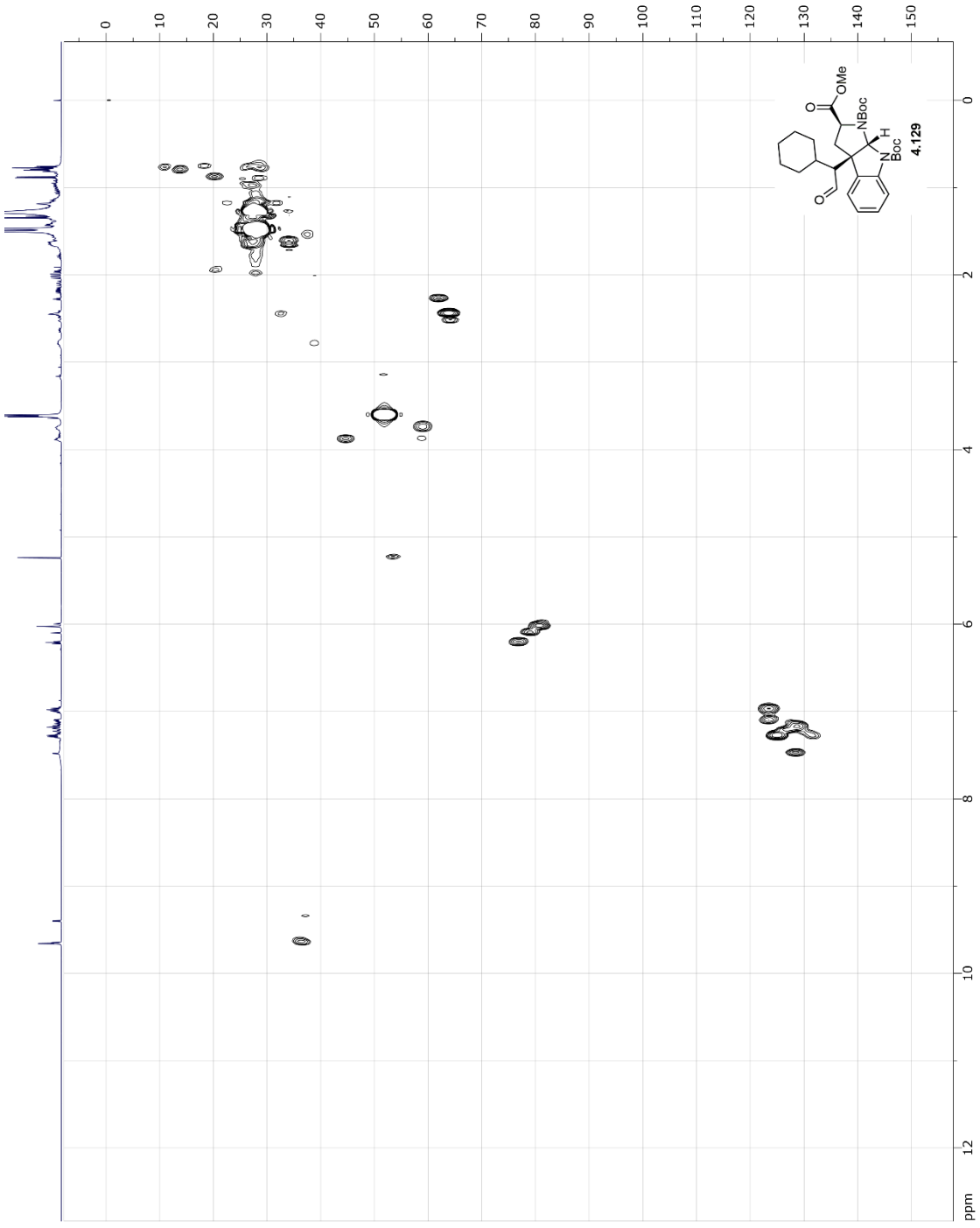

OMe
NBoc
H
N
H
Boc
O
O
4.132
ppm

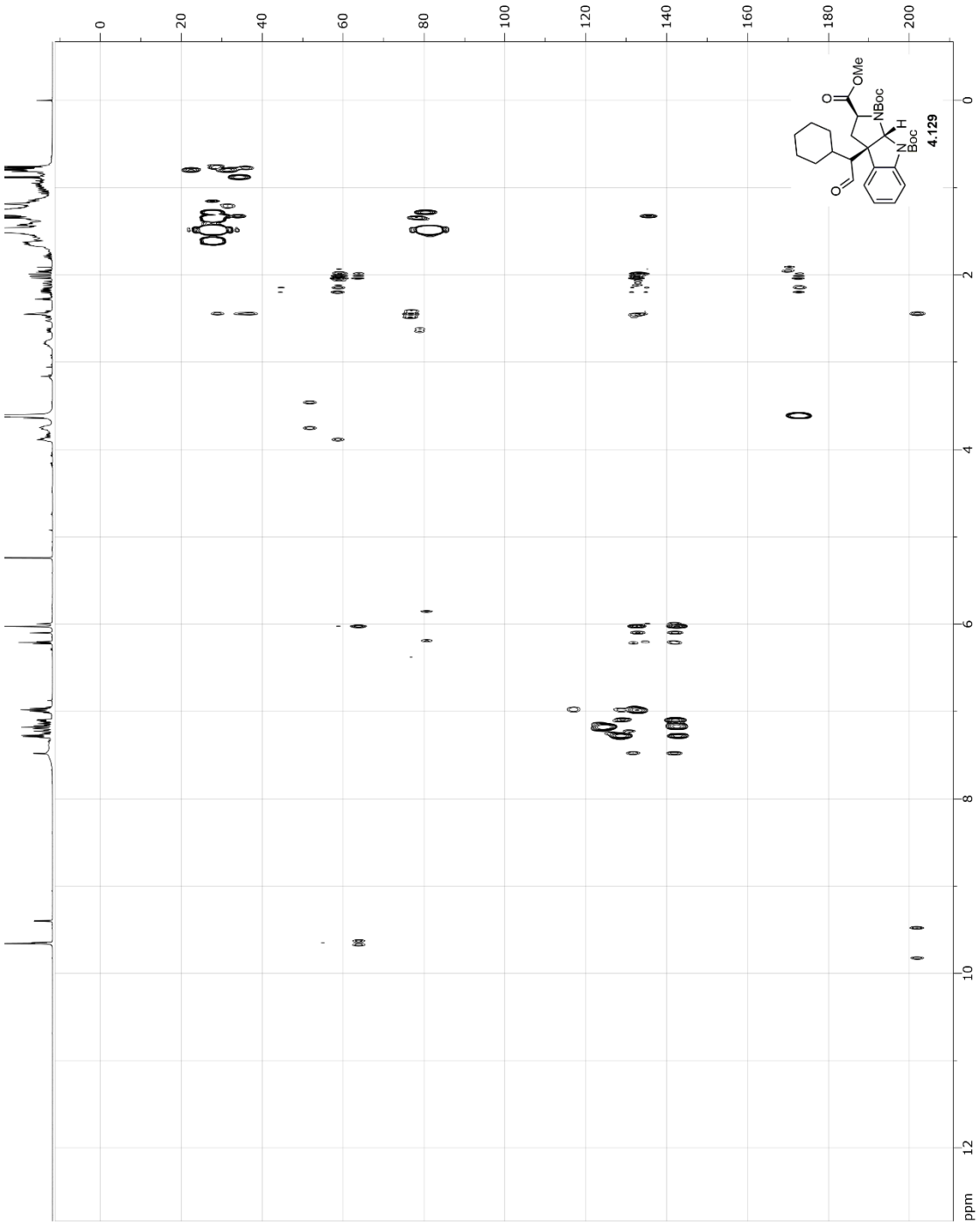

0
20
40
60
80
100
120
140
160
180
200
0
1
2
3
4
5
6
7
8
ppm
OMe
NBoc
H
N
Boc
O
4.132

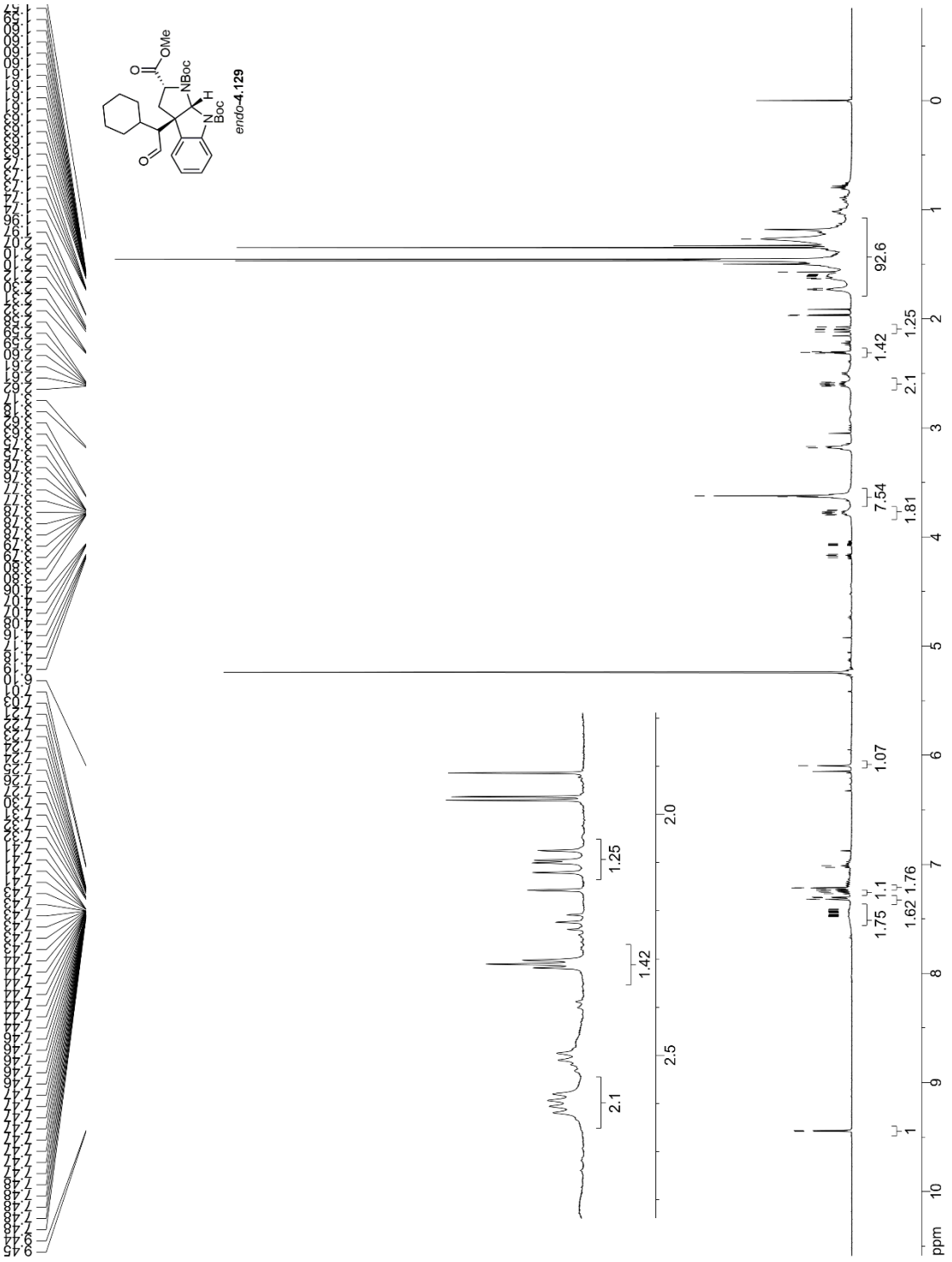

OMe
O
NBoc
H
O
O
H
N
Boc
4.132
1.40
1.40
1.41
1.41
1.41
1.58
2.50
2.53
2.53
2.56
3.75
6.33
7.87
ppm

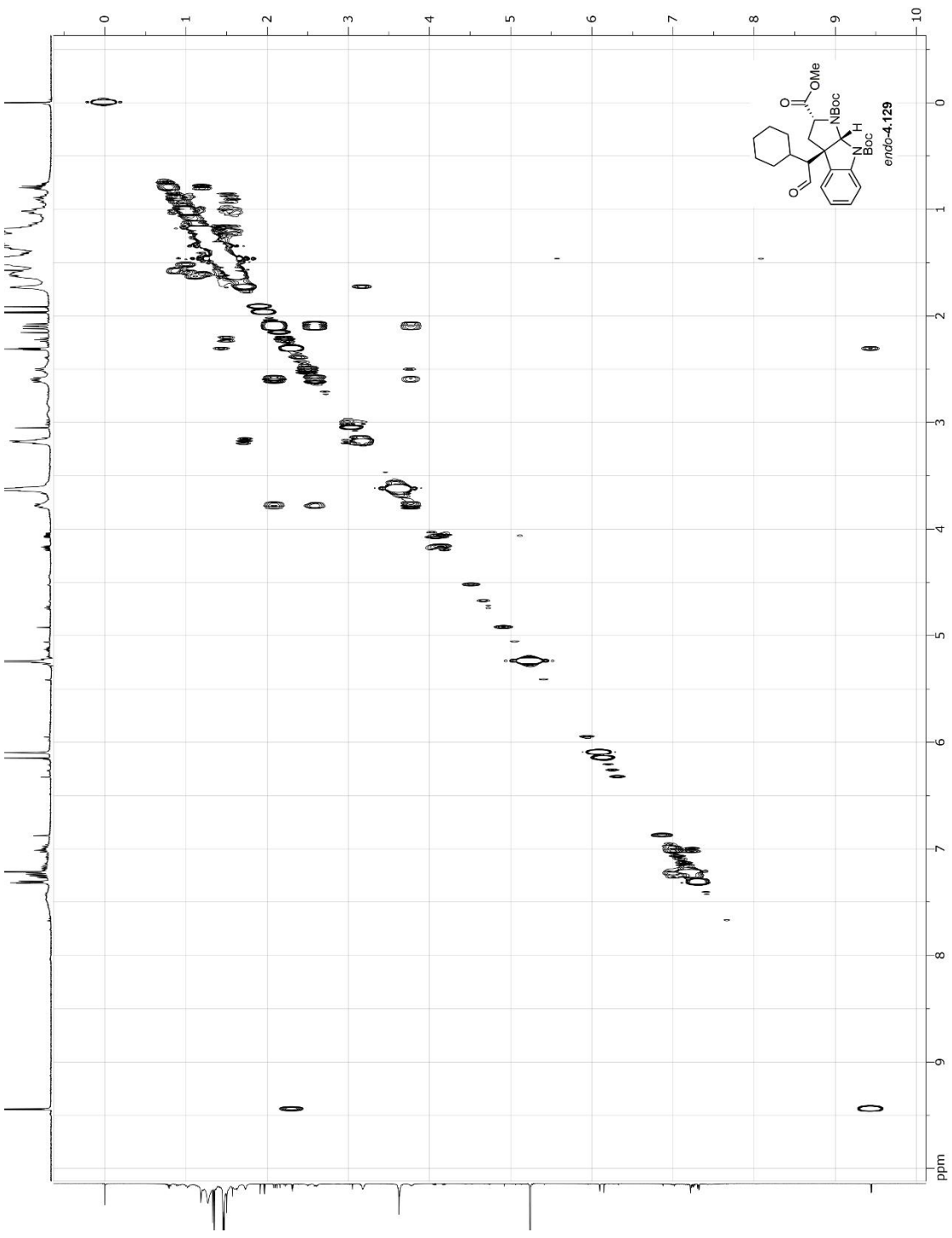

OMe
NBoc
H
N
Boc
4.129
1.18
0.847
2.0
2.5
1.07
3.0
0.761
1.05
1.2
1.31
1.52
1
2.9
1.35
1.18
1.07
3.38
0.847
54.4
ppm

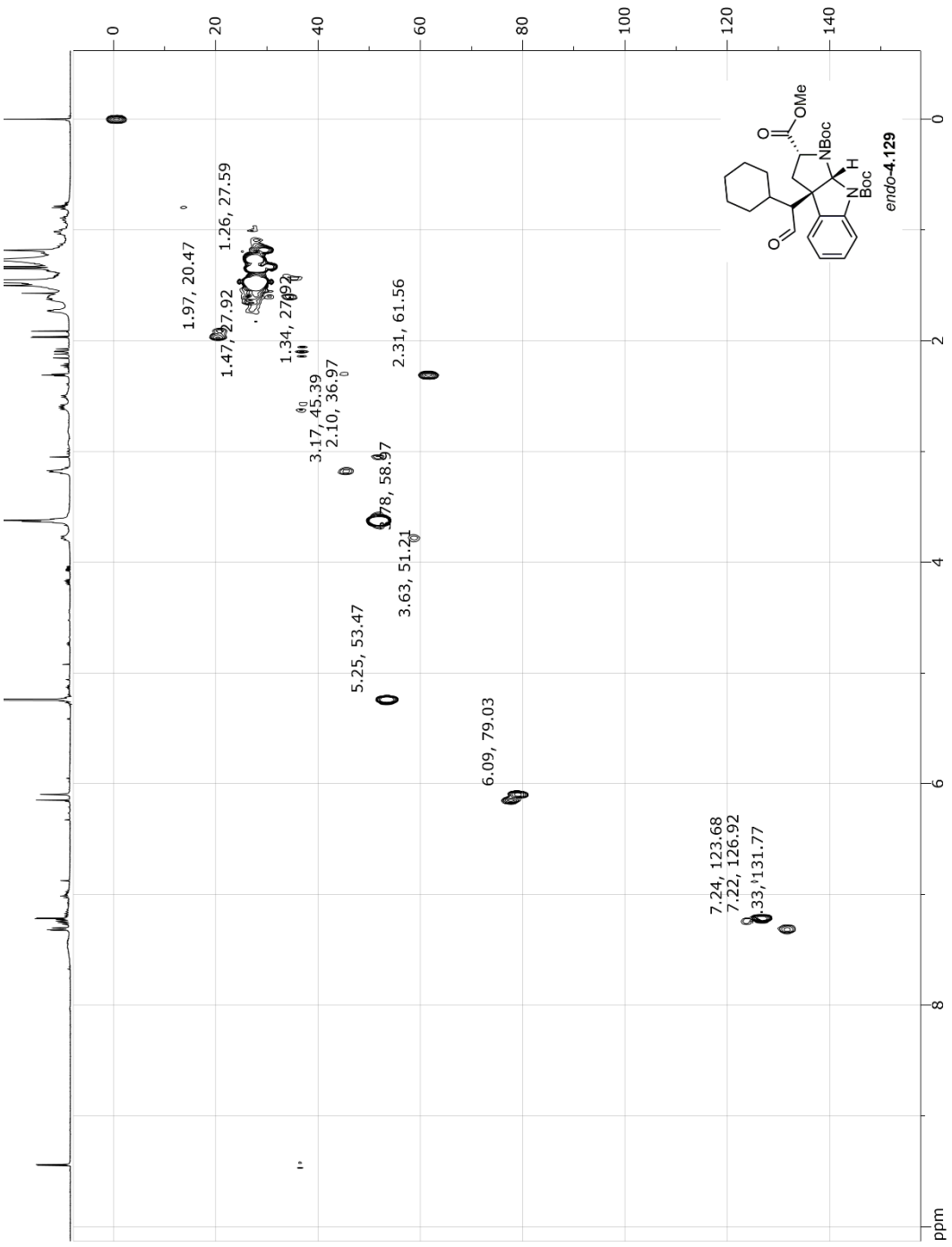

OMe
NBoc
H
N
Boc
4.129
ppm

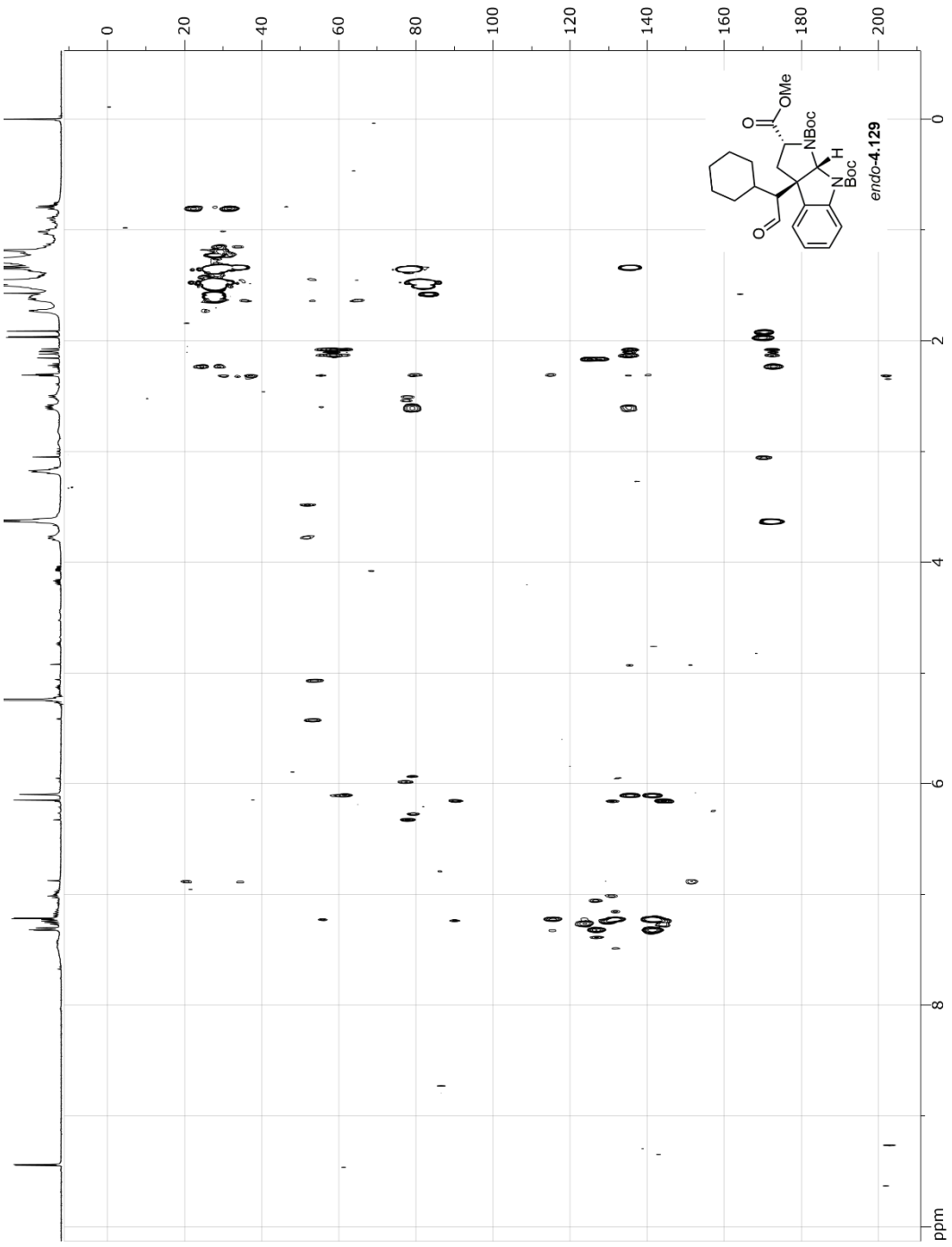

OMe
NBoc
H
Boc
4.129
ppm

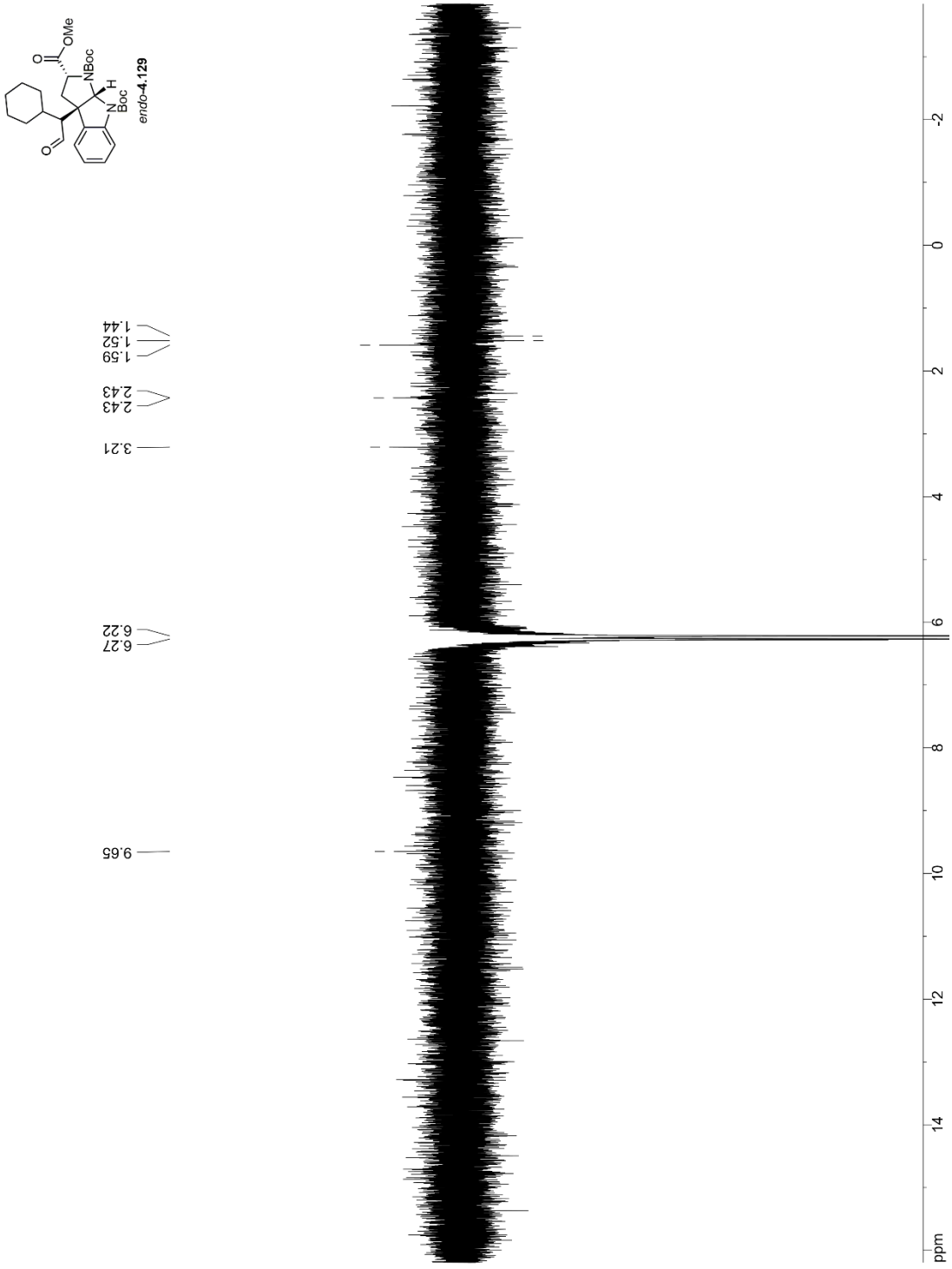

OMe
NBoc
H
N
Boc
O
O
4.129
0
20
40
60
80
100
120
140
160
180
200
0
2
4
6
8
10
12
ppm

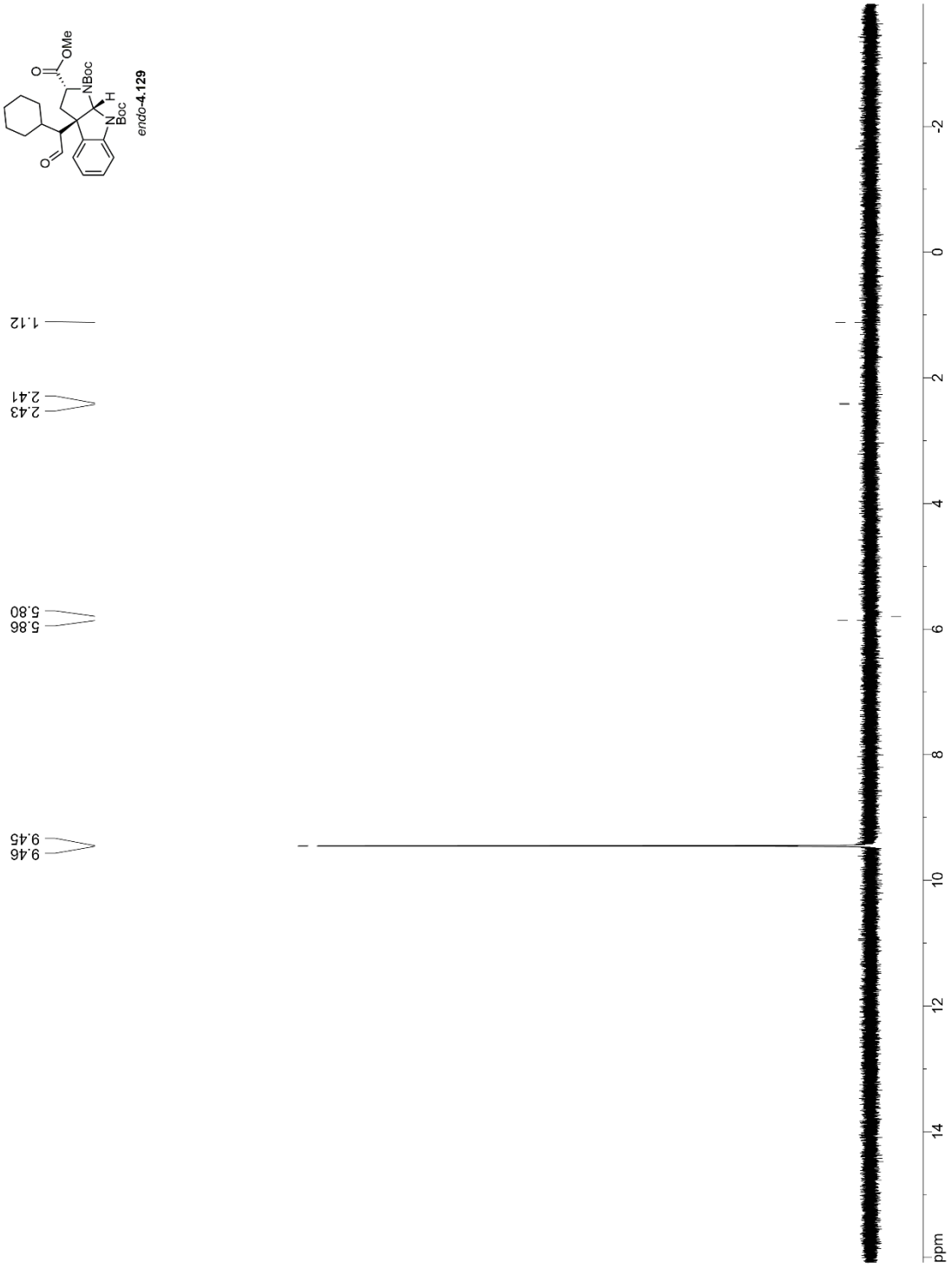

OMe
NBoc
H
N
Boc
O
O
endo-4.129
92.6
1.42
1.25
2.1
7.54
1.81
1.07
2.1
1.25
2.0
1.42
2.5
1.75
1.1
1.62
1.76
1
ppm

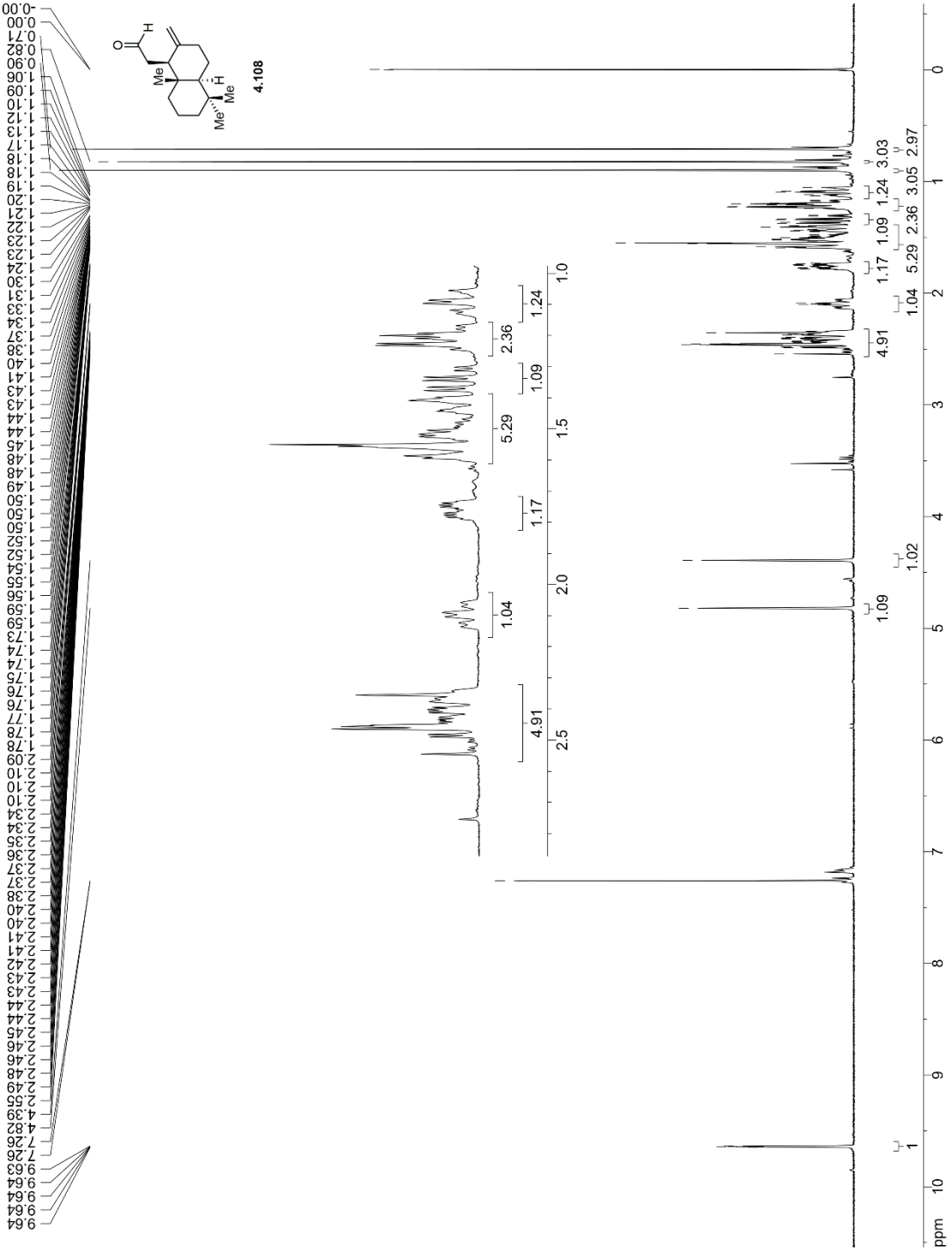

OMe
NBoc
H
N
Boc
O
O
endo-4.129
ppm

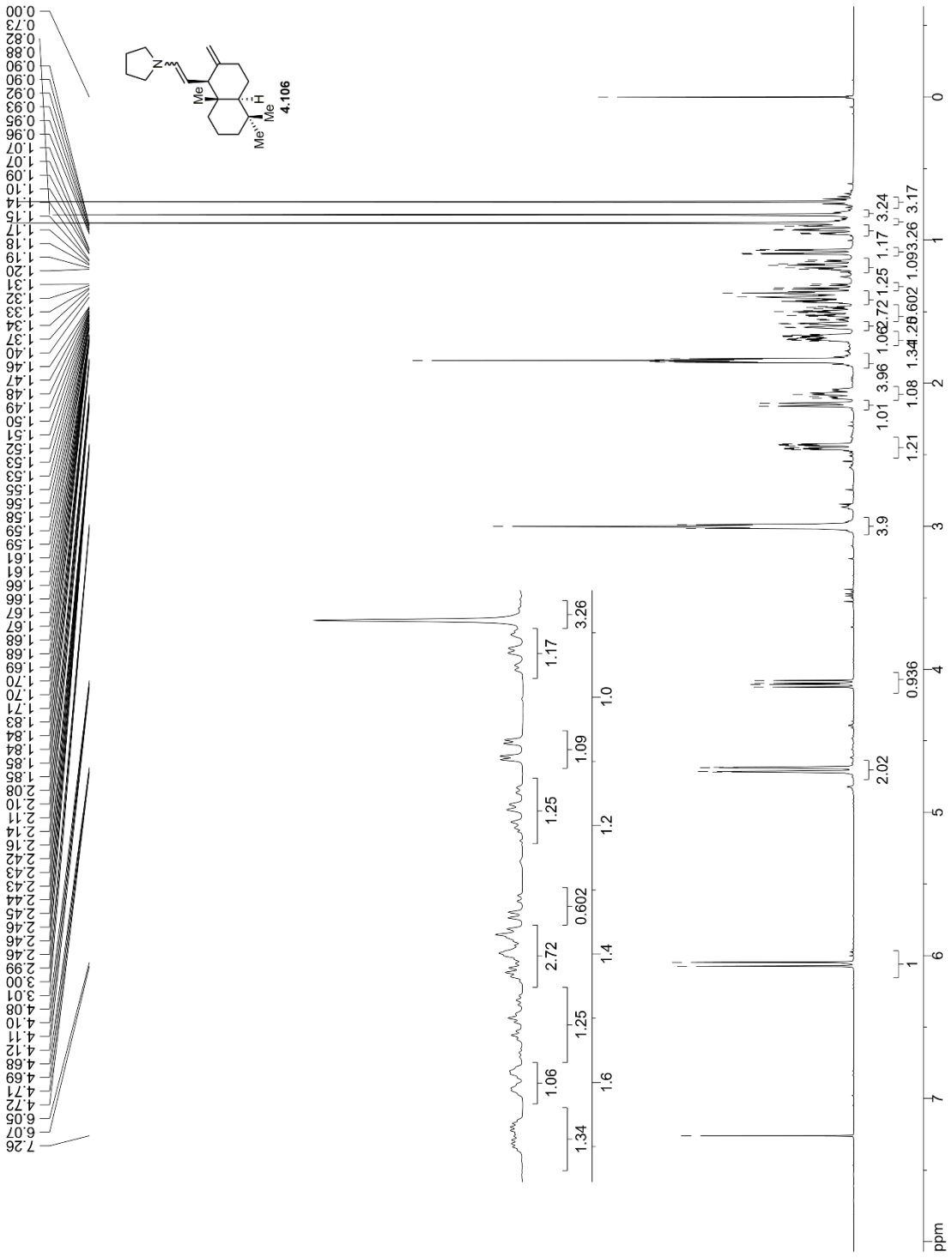

1.97, 20.47
1.47, 27.92
1.26, 27.59
1.34, 27.92
3.17, 45.39
2.10, 36.97
2.31, 61.56
5.25, 53.47
3.63, 51.21
6.09, 79.03
7.24, 123.68
7.22, 126.92
7.33, 131.77
OMe
NBoc
H
N
Boc
O
O
endo-4.129
ppm

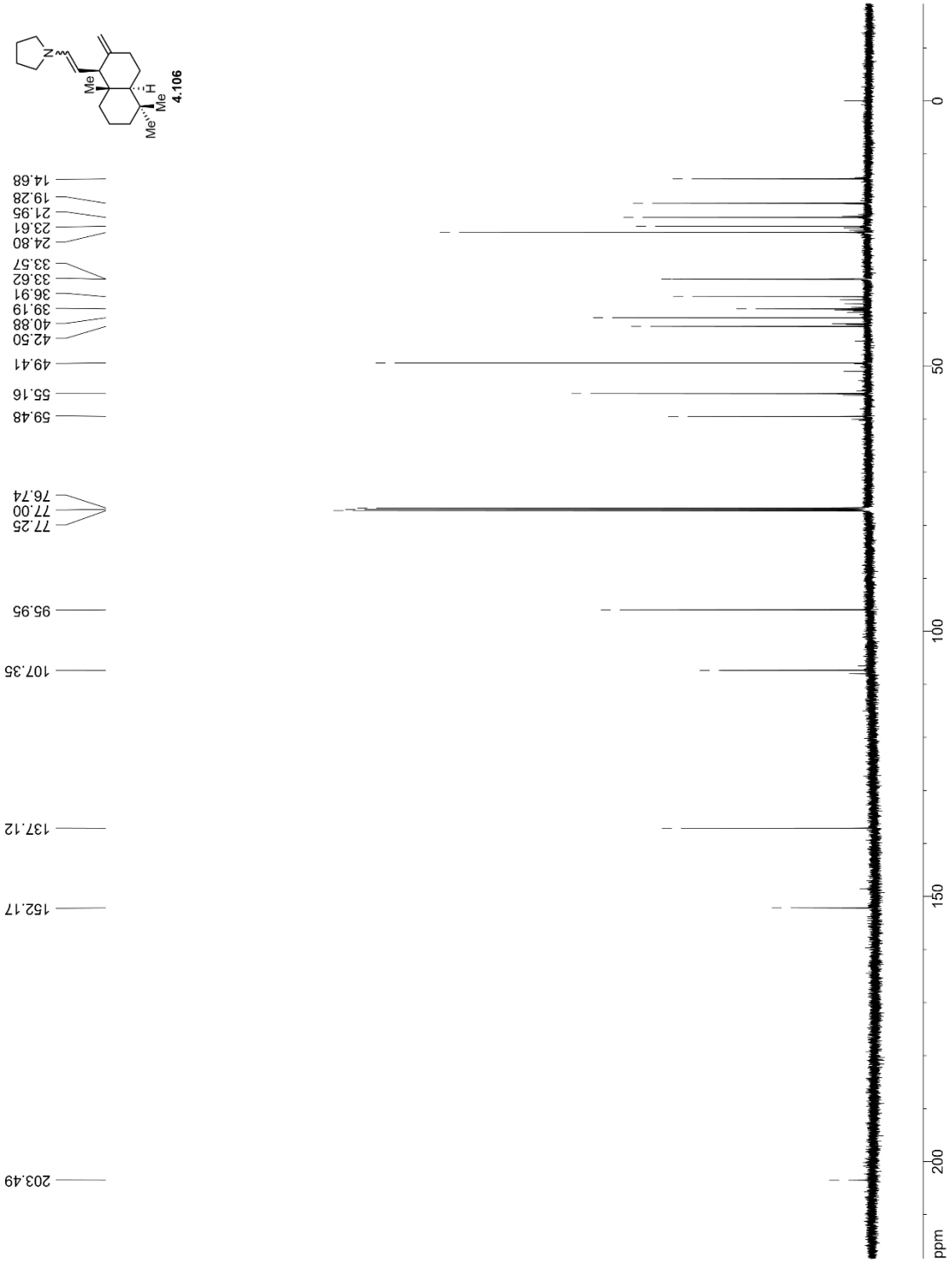

0
20
40
60
80
100
120
140
160
180
200
ppm
0
2
4
6
8
OMe
O
NBoc
H
N
Boc
O
endo-4.129


OMe
O
NBoc
H
N
Boc
O
endo-4.129
1.44
1.52
1.59
2.43
2.43
3.21
6.22
6.27
9.65
ppm
-2
0
2
4
6
8
10
12
14


OMe
O
NBoc
H
N
Boc
O
*endo*-**4.129**
1.12
2.43
2.41
5.86
5.80
9.46
9.45
-2
0
2
4
6
8
10
12
14
ppm


4.108
Me
Me
H
Me
H
O
ppm


Me
Me
Me
H
4.106
ppm


Me
H
Me
Me
4.106
14.68
19.28
21.95
23.61
24.80
33.57
33.62
36.91
39.19
40.88
42.50
49.41
55.16
59.48
76.74
77.00
77.25
95.95
107.35
137.12
152.17
203.49
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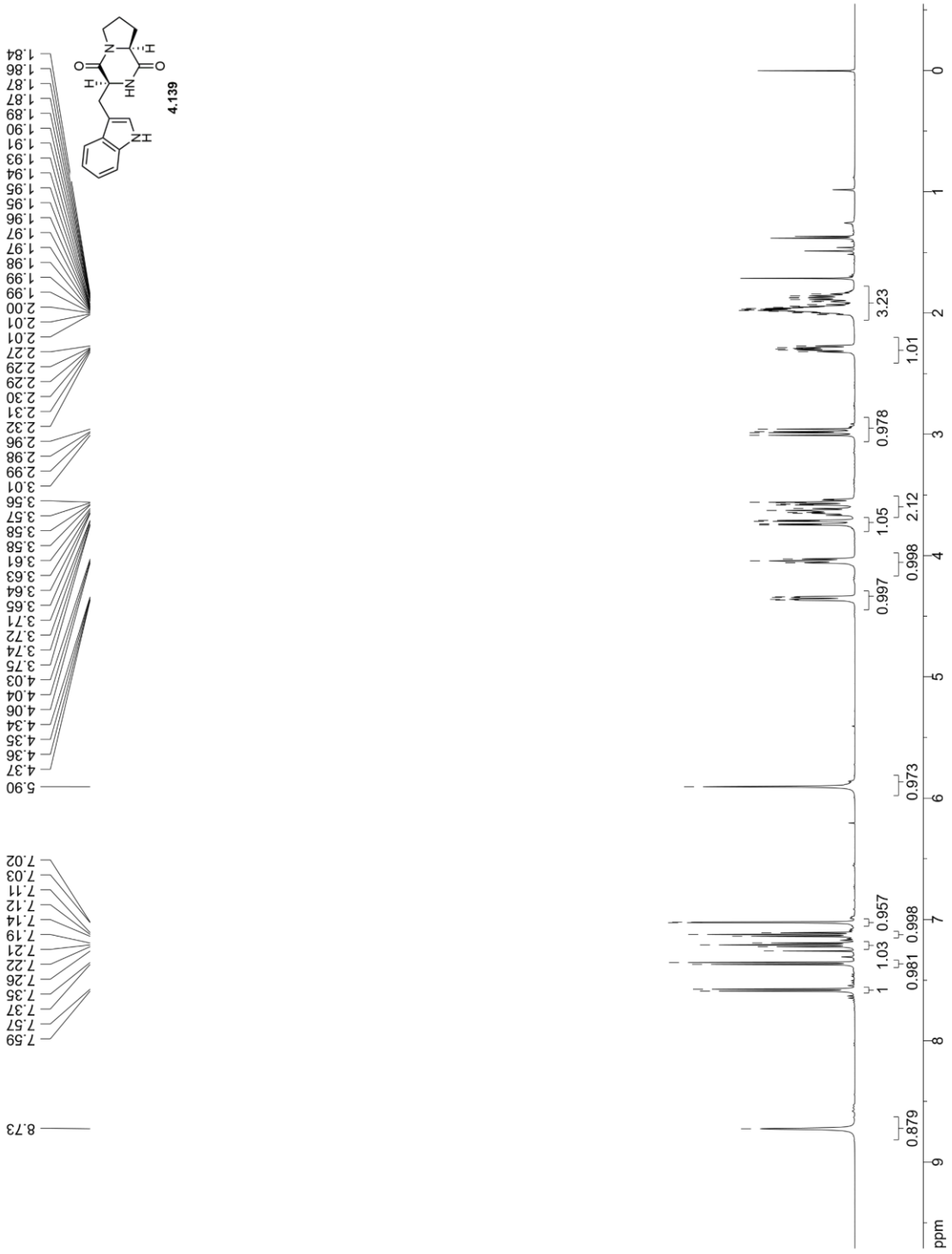
50
100
150
200
ppm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1.89
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1.91
1.93
1.94
1.95
1.95
1.96
1.97
1.97
1.98
1.99
1.99
2.00
2.01
2.01
2.27
2.29
2.29
2.30
2.31
2.32
2.96
2.98
2.99
3.01
3.56
3.57
3.58
3.58
3.61
3.63
3.64
3.65
3.71
3.72
3.74
3.75
4.03
4.04
4.06
4.34
4.35
4.36
4.37
5.90
7.02
7.03
7.11
7.12
7.14
7.19
7.21
7.22
7.26
7.35
7.37
7.57
7.59
8.73
0.879
1
1.03
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0.998
0.973
0.997
0.998
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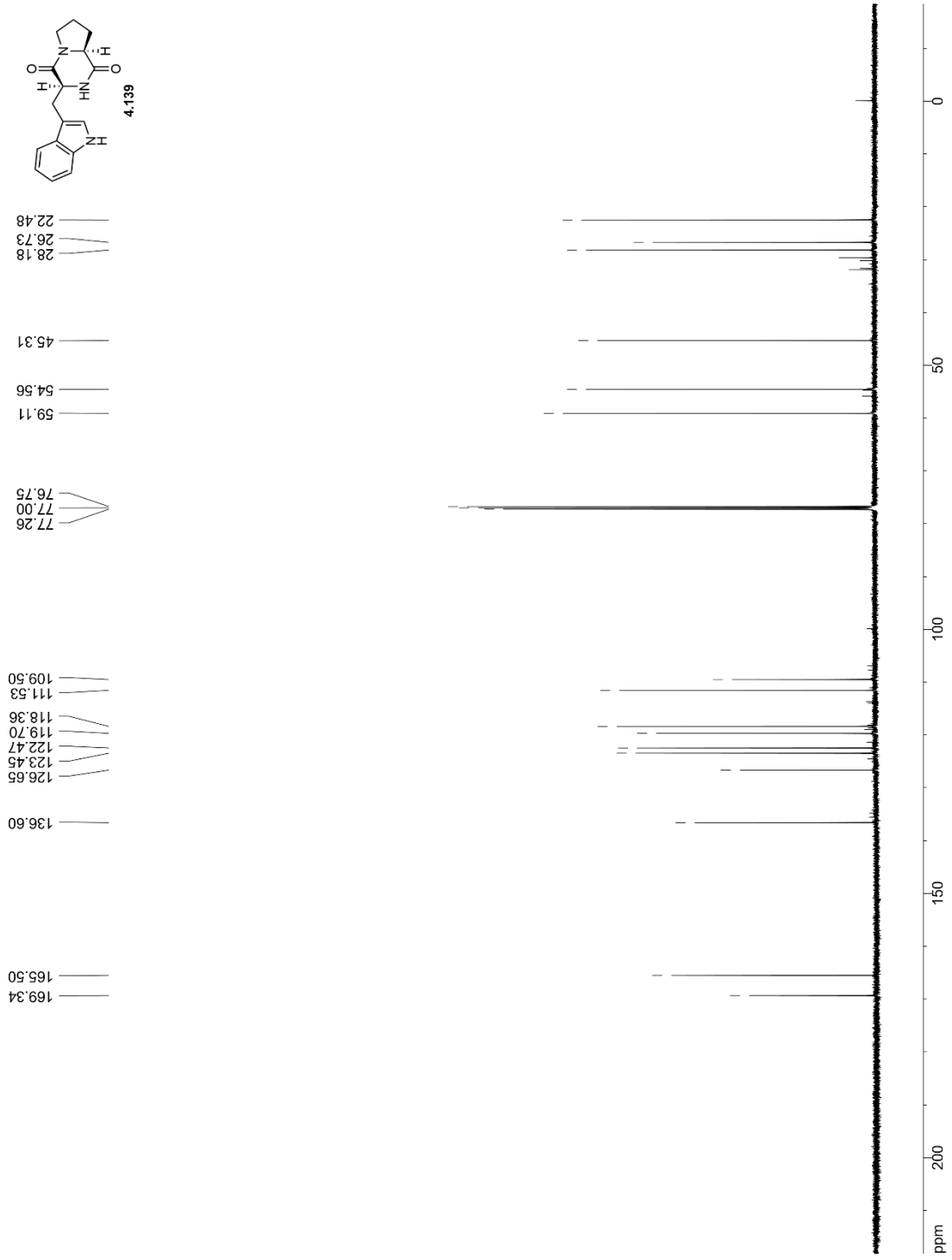
0.978
2.12
1.01
3.23
ppm


4.139
22.48
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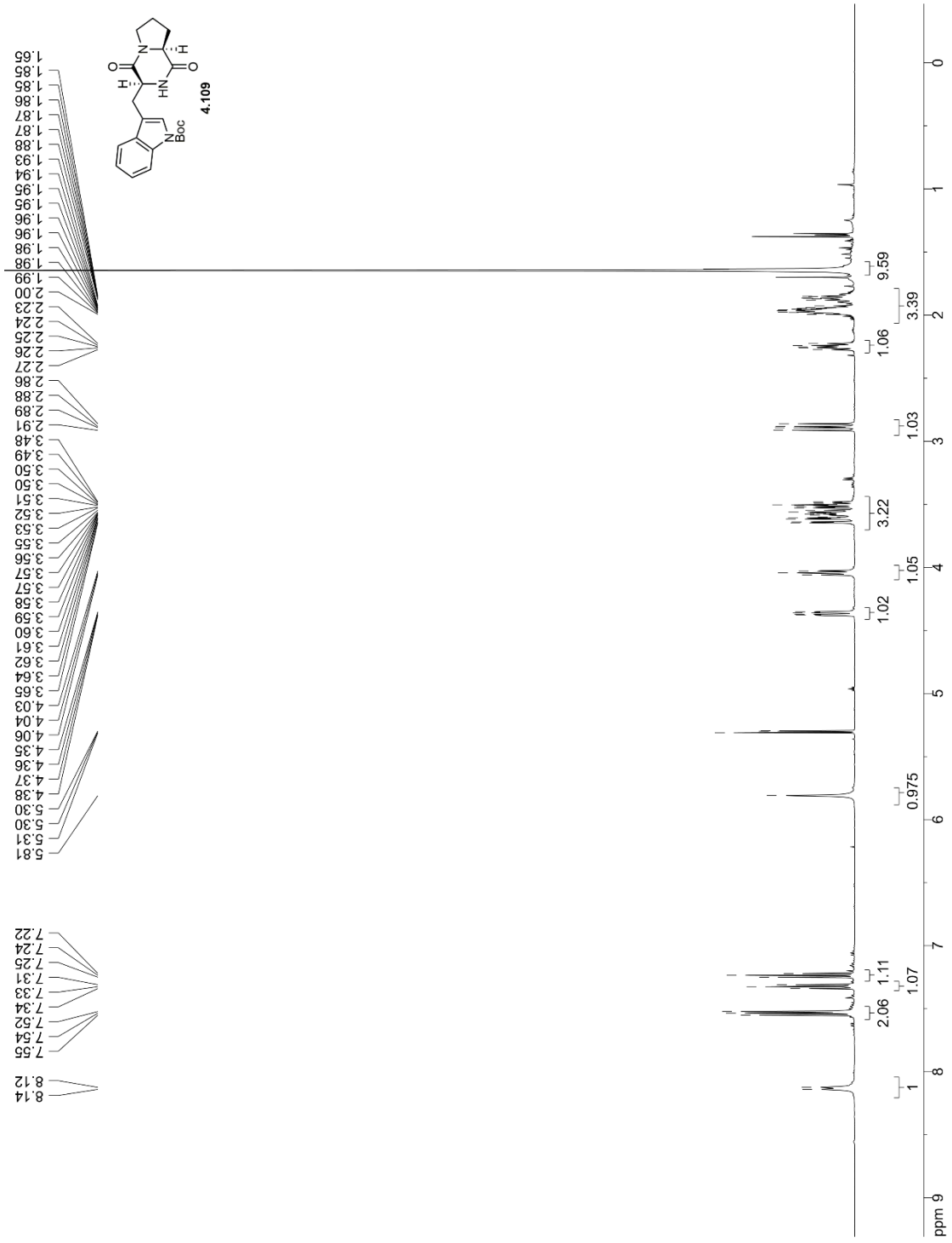
45.31
54.56
59.11
76.75
77.00
77.26
109.50
111.53
118.36
119.70
122.47
123.45
126.65
136.60
165.50
169.34
0
50
100
150
200
ppm


4.109
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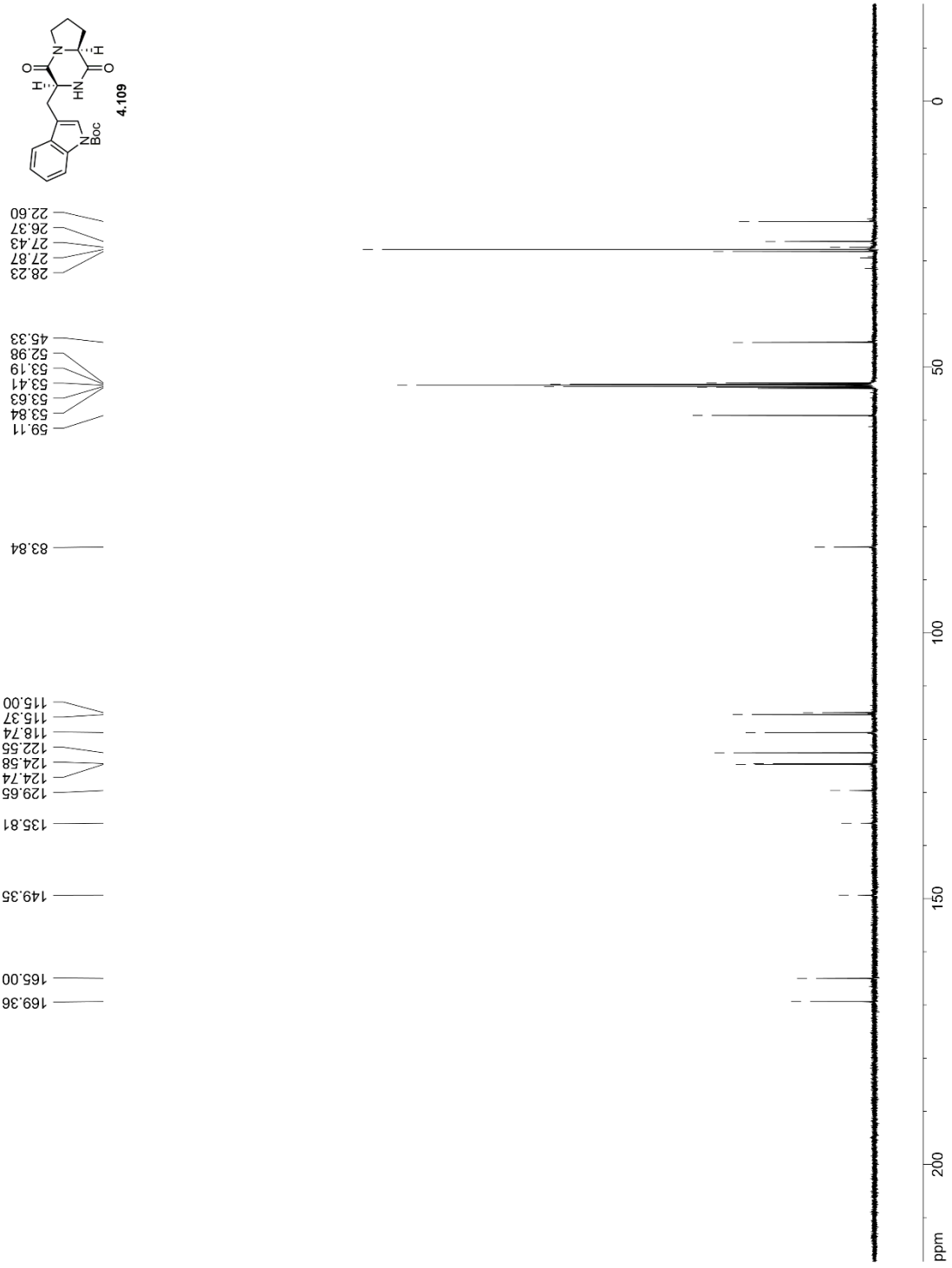
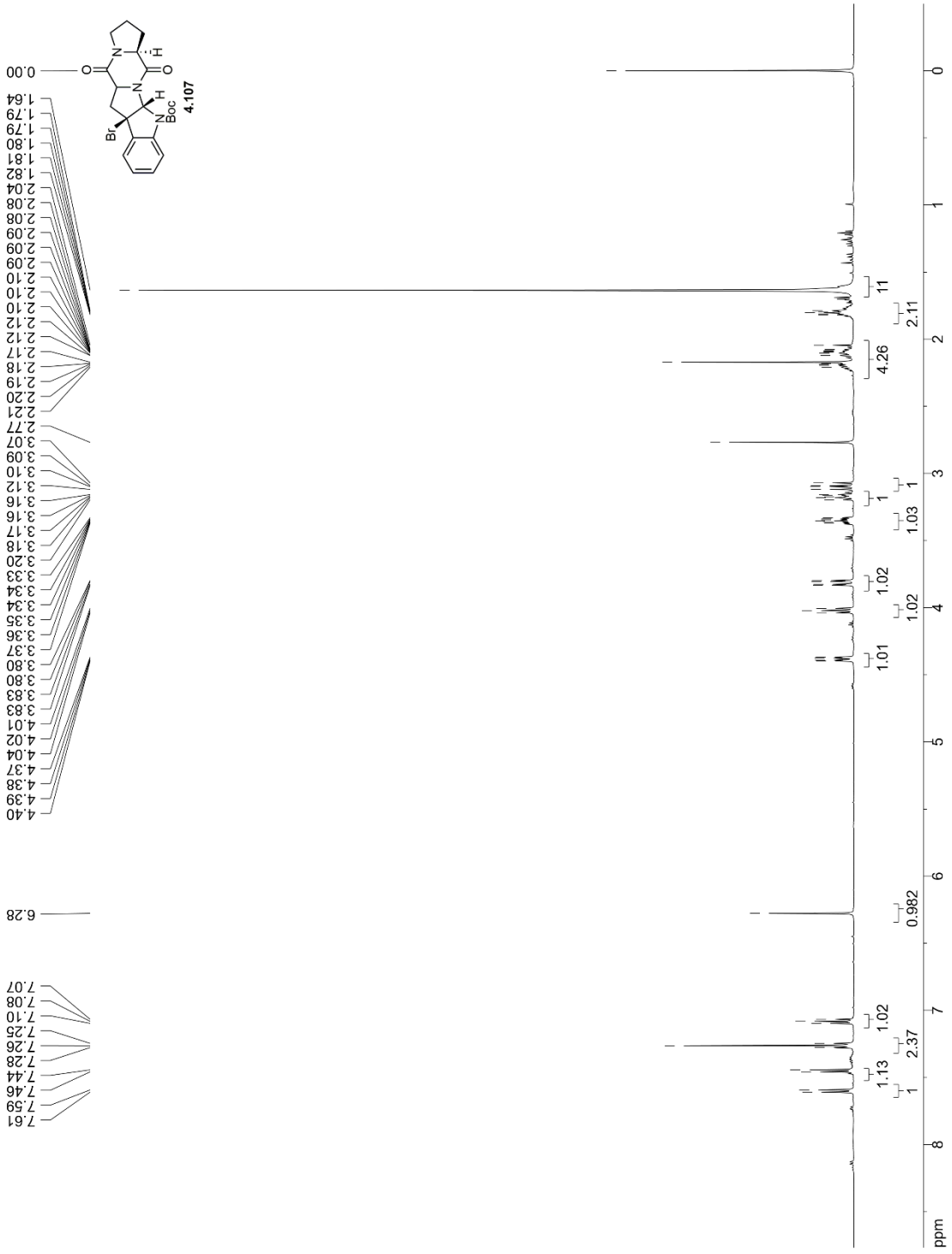
1.85
1.86
1.87
1.87
1.88
1.93
1.94
1.95
1.95
1.96
1.96
1.98
1.98
1.99
2.00
2.23
2.24
2.25
2.26
2.27
2.86
2.88
2.89
2.91
3.48
3.49
3.50
3.50
3.51
3.52
3.53
3.55
3.56
3.57
3.57
3.58
3.59
3.60
3.61
3.62
3.64
3.65
4.03
4.04
4.06
4.35
4.36
4.37
4.38
5.30
5.30
5.31
5.81
7.22
7.24
7.25
7.31
7.33
7.34
7.52
7.54
7.55
8.12
8.14
2.06
1.11
1.07
1
0.975
1.02
1.05
3.22
1.03
1.06
3.39
9.59
ppm


4.109
22.60
26.37
27.43
27.87
28.23
45.33
52.98
53.19
53.41
53.63
53.84
59.11
83.84
115.00
115.37
118.74
122.55
124.58
124.74
129.65
135.81
149.35
165.00
169.36
0
50
100
150
200
ppm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1.82
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2.08
2.08
2.09
2.09
2.09
2.10
2.10
2.10
2.12
2.12
2.17
2.18
2.19
2.20
2.21
2.77
3.07
3.09
3.10
3.12
3.16
3.16
3.17
3.18
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3.35
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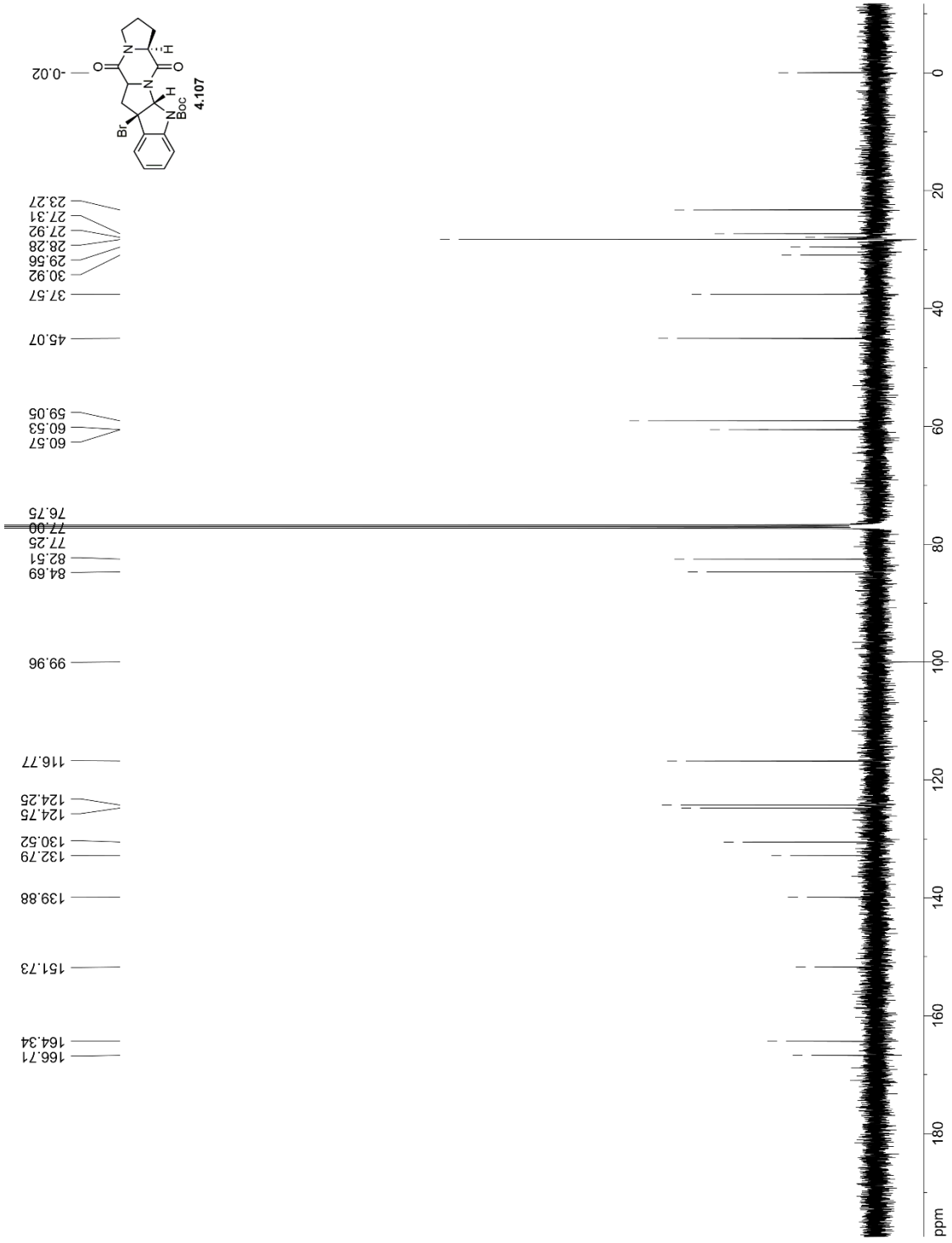
3.80
3.83
3.83
4.01
4.02
4.04
4.37
4.38
4.39
4.40
6.28
7.07
7.08
7.10
7.25
7.26
7.28
7.44
7.46
7.59
7.61
11
2.11
4.26
1
1.03
1.02
1.02
1.01
0.982
1.02
1.13
2.37
1
ppm


4.107
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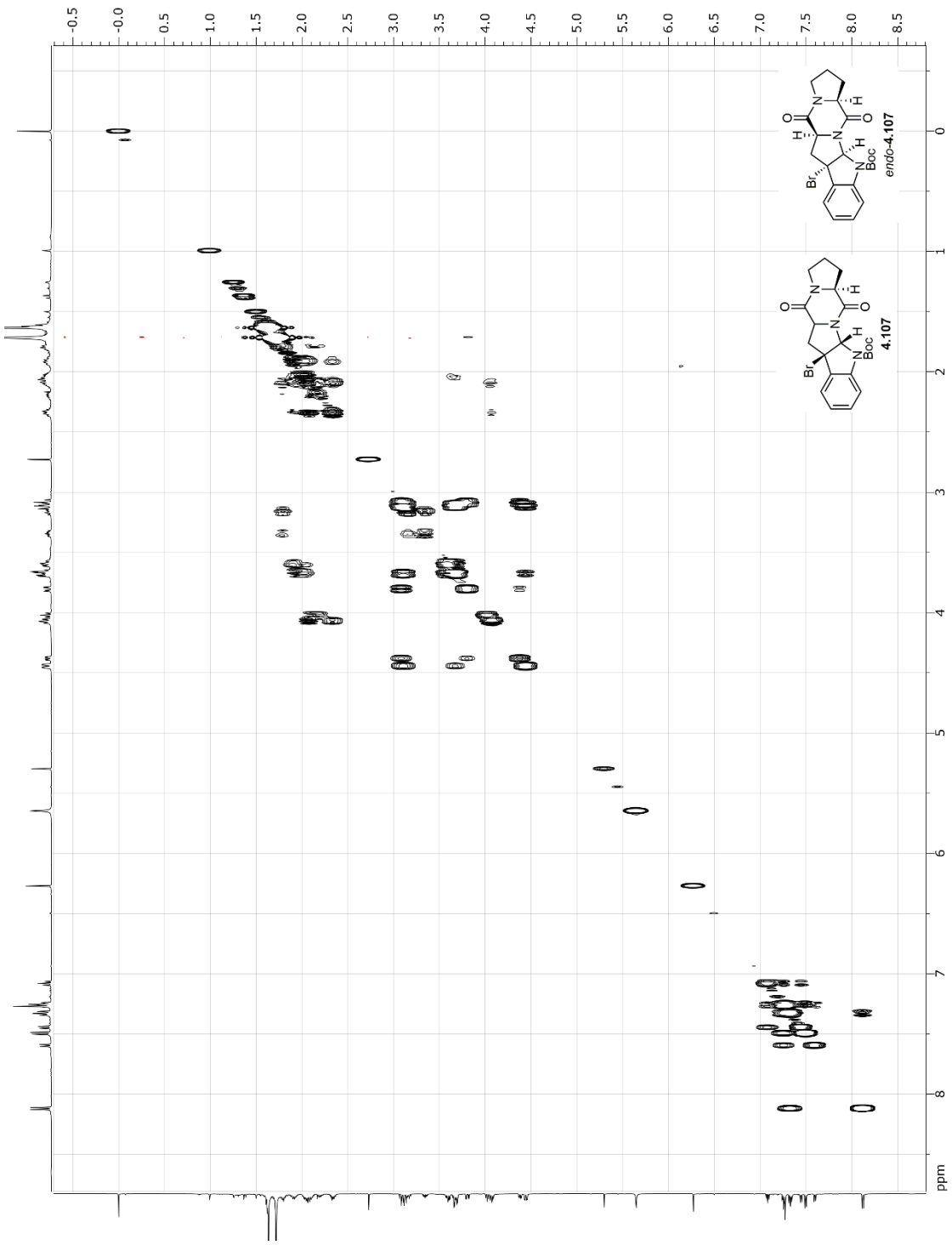
27.92
28.28
29.56
30.92
37.57
45.07
59.05
60.53
60.57
76.75
77.00
77.25
82.51
84.69
99.96
116.77
124.25
124.75
130.52
132.79
139.88
151.73
164.34
166.71
0
20
40
60
80
100
120
140
160
180
ppm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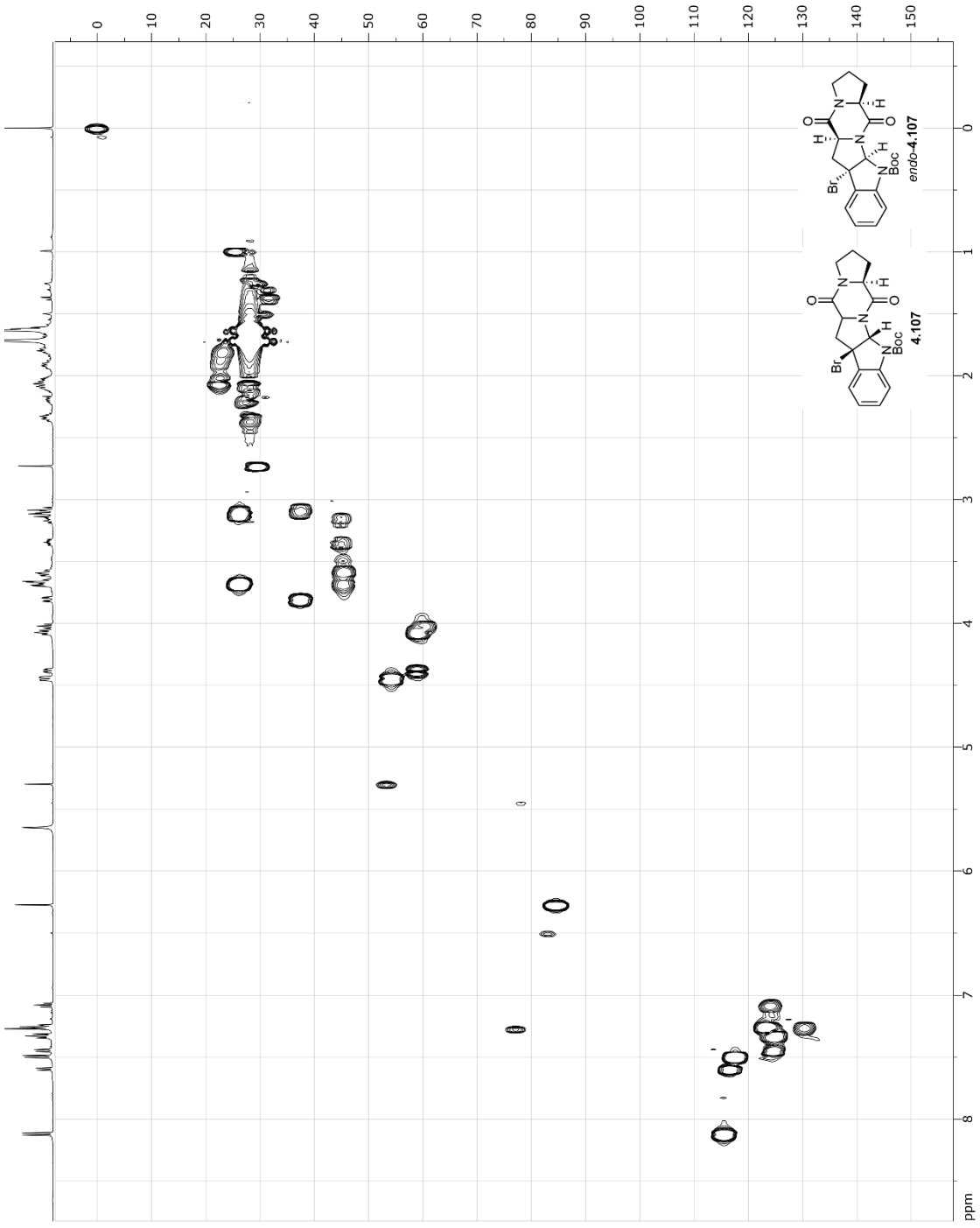
ppm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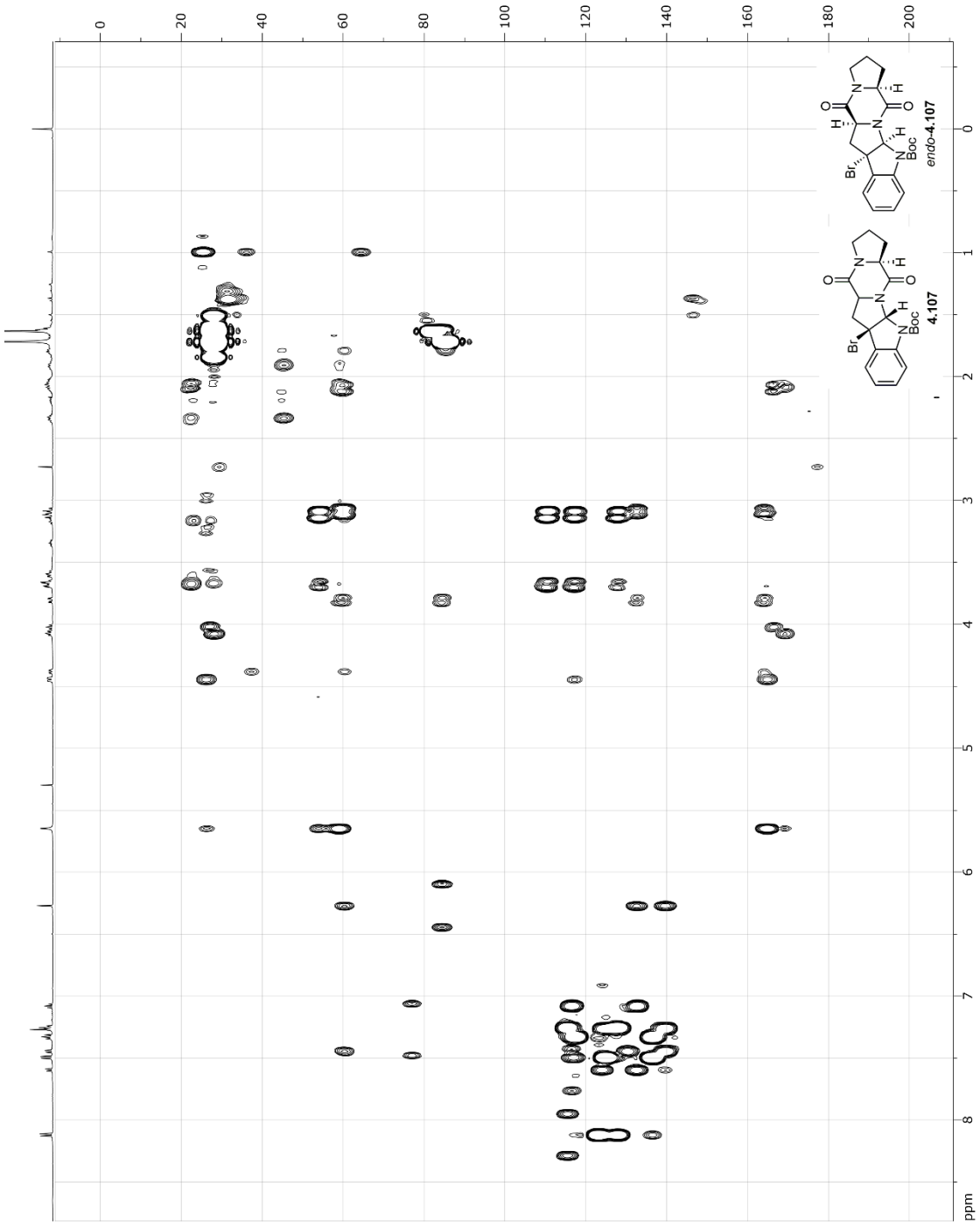
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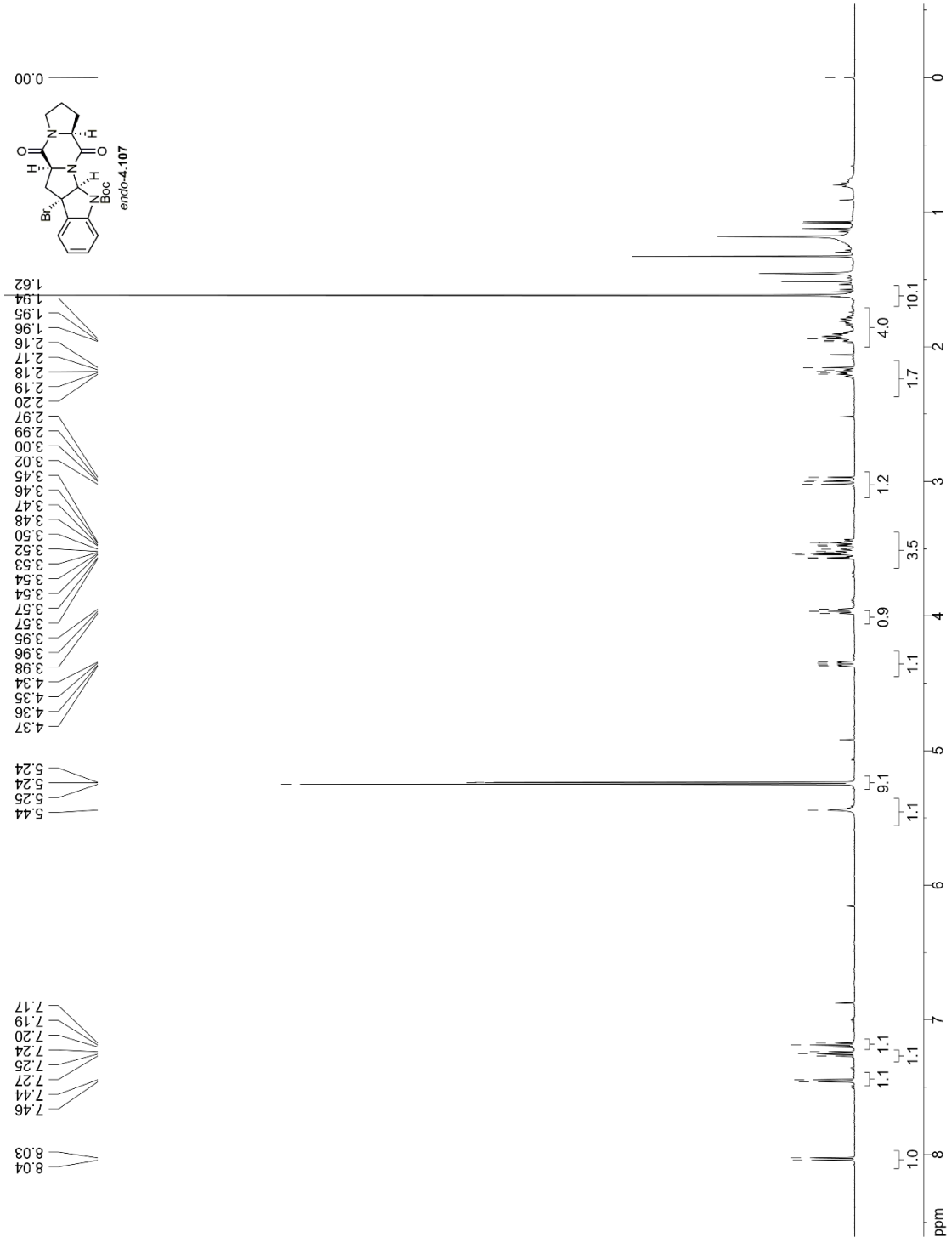
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1.96
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2.17
2.18
2.19
2.20
2.97
2.99
3.00
3.02
3.45
3.46
3.47
3.48
3.50
3.52
3.53
3.54
3.54
3.57
3.57
3.95
3.96
3.98
4.34
4.35
4.36
4.37
5.24
5.24
5.25
5.44
7.17
7.19
7.20
7.24
7.25
7.27
7.44
7.46
8.03
8.04
10.1
4.0
1.7
1.2
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0.9
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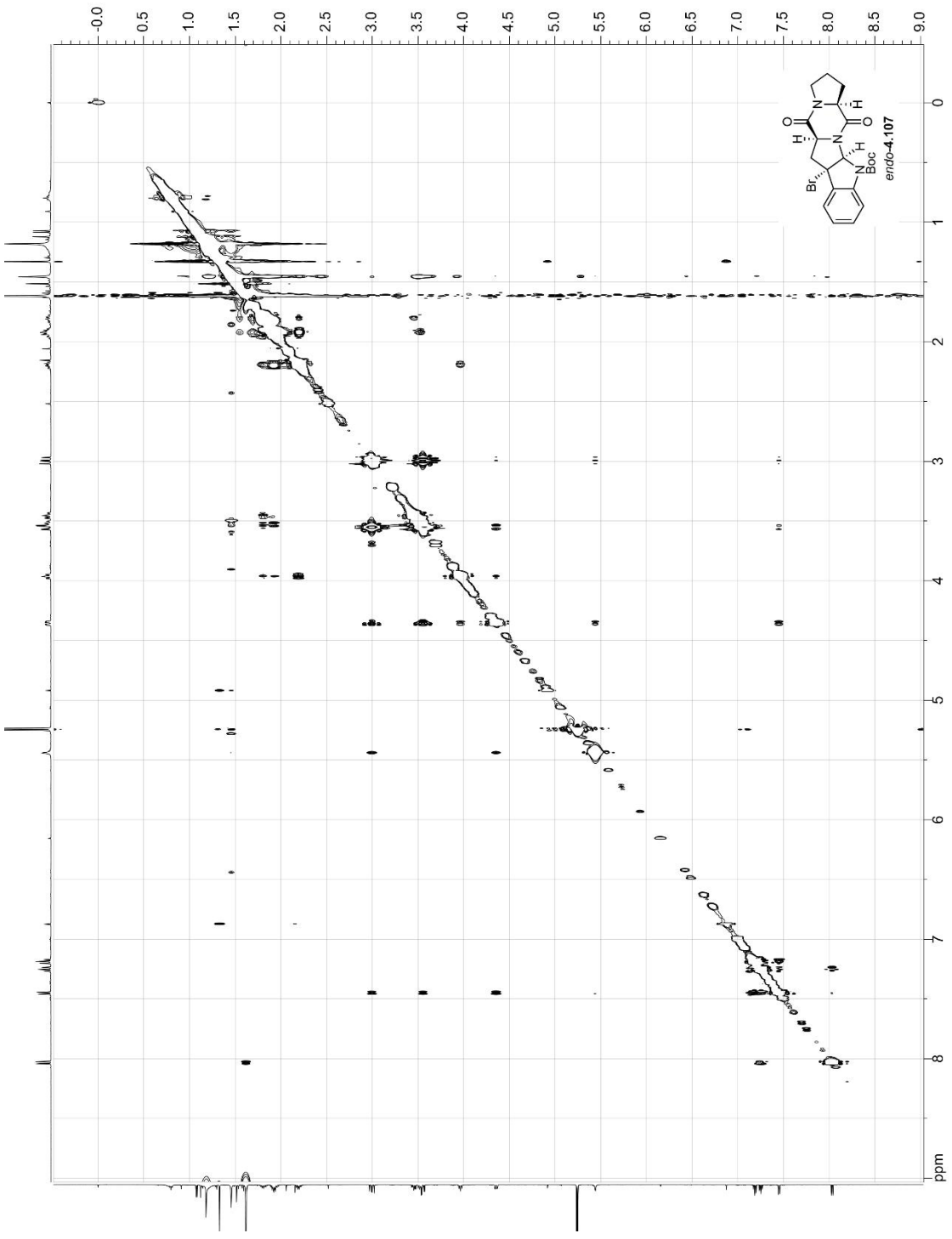
9.1
1.1
1.1
1.1
1.1
1.1
1.0
ppm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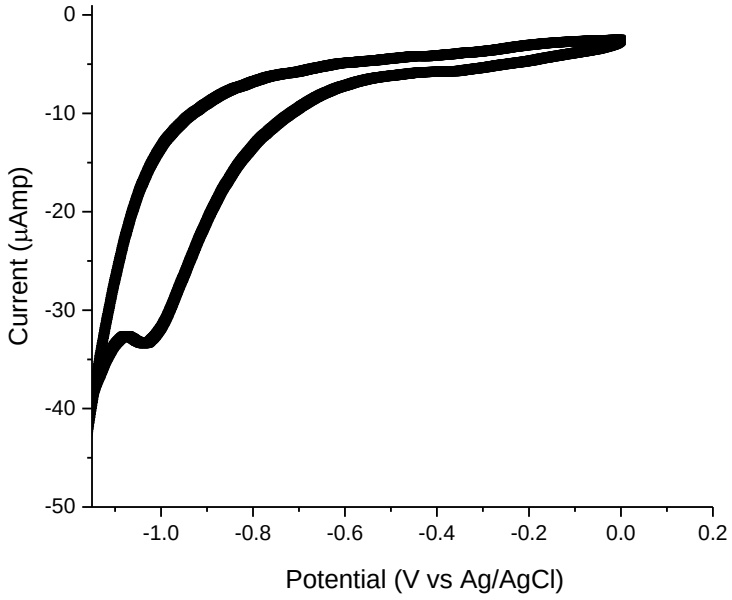


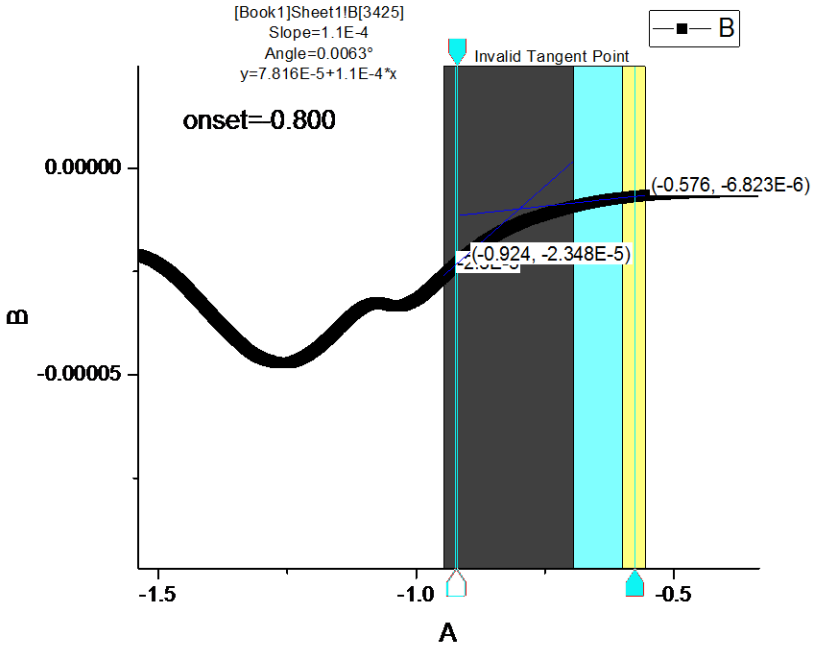


**Cyclic voltammetry of bromopyrroloindoline 4.5**